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HEALTH DIVISION
GAMMA-RAY SPECTROSCOPY GROUP
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Division Director

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RADIUM-INDUCED MALIGNANT TUMORS IN MAN*

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Abstract

The incidence of radium-induced malignant tumors and blood dyscrasias was related to current or preterminal radium burden measurements and to retrospective estimates of maximum radium burdens for a series of 293 persons, most of whom acquired radium burdens in the period 1918 to 1933. The 46 malignant diseases included 23 bone sarcomas, 16 neoplasms of the skull (principally mastoid and paranasal air cell carcinomas), and 7 leukemias and aplastic anemias. Retrospective estimates of maximum radium burdens were made by application of the appropriate power function for ingestion or for multiple injections. The power function parameters used here ($\underline{a}$ = 0.30 and $\underline{b}$ = -0.44) were recently derived by an analysis of data from long-term studies on 8 patients for whom suitable data are available. The lowest estimated maximum radium burden for the bone sarcoma cases was 6.72 μCi, and that for carcinoma of the maxilla was 1.23 μCi. The comparable value for radium attributed leukemias and other blood dyscrasias was over 50 μCi. Based on the estimated maximum initial burden, these data imply at least a twelvefold margin of safety in the maximum permissible level for internally deposited radium.

Introduction

For many years we have been engaged in an investigation of the long-term effects of radium deposition in man. For the present symposium we have been asked to review and interpret our data as they bear on the subject of radium-induced malignant tumors. As a result of this emphasis on oncogenesis, this contribution will be highly selective and will not attempt to cover many other aspects of the consequences of radium deposition in skeletal tissues viewed after a considerable lapse of time.

We have a photograph of a group of radium dial painters taken in 1925 in a "radium studio" in a town that lies within 100 miles of Chicago. Within a rather large room there are 6 rows of young women seated at individual school-type desks with 9 to 12 desks per row. Of the 67 persons in the photograph, 14 have not been identified and are not known, and 9 have been identified but have not been studied. We are fairly certain that we

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know the names of 9 of these 14 unidentified persons, but the names have not been matched with the faces. The remaining 44 women have either been studied by us within the past 10 years or are otherwise known to be well or to have had a specific disease. Among these 44 cases, there are 16 who are no longer alive, and 7 of these 16 had malignant diseases attributable to radium, and 5 had malignancies presumably unrelated to radium. Among the 28 persons who are still alive in September 1967, there is one woman who has had two different malignant tumors attributable to radium. For the population represented in the 1925 photograph, then, there are 8 known cases among 67, or 11.9%, who have developed malignant tumors ascribable to radium.

By way of contrast, we have another photograph taken in a second dial painting company in the same town in 1935, ten years later. Here there are 32 young women, 7 of whom were also in the 1925 picture. We have studied 20 of these dial painters, and of the 12 that were not studied we have been unable to identify 6. Of these 20 that were studied, 15 are still alive and are in reasonably good health, and 5 have died, all of malignant tumors. Among these 5 deaths there are 3 cases with malignant disease attributable to radium. However, 2 of these cases were also present in the 1925 picture and the third person was known to have started work in 1924. When the latter 3 cases are deleted, we have for the new faces a known incidence of $0/17 = 0\%$ malignancies ascribable to radium.

The reasons for this striking difference may be many, but the 10-year average age difference is not the principal one. In the group that appeared exclusively in the 1935 picture, current or preterminal body burdens of radium range from <0.001 to 0.020 μCi for those who started to work after 1926. The comparable range is 0.028 to 18.0 μCi for those women in the 1935 photograph who started to work before 1926. The principal cause for this difference is the fact that tipping or pointing the radium-laden brush between the lips was discontinued as an acceptable practice on or about January 1, 1926 as far as we have been able to ascertain. As a result of this change radium was acquired internally only to a very slight extent after this date. The largest body burden that we have seen in a dial painter who started to work after 1930 is 0.033 μCi in a woman who worked from July 1943 through July 1951. Twelve dial painters whose employment in the second plant began in the 1930's and 1940's had radium burdens ranging from <0.001 to 0.033 μCi when they were measured in the Argonne National Laboratory whole-body counter in 1957-1959. Because of the low radium burdens in this more recently employed group, we have concentrated our attention largely on those persons who worked before 1930.

Population Available for Study

Although the largest group of cases that we have studied was exposed occupationally, the cases have been drawn from two principal sources:

industrial and iatrogenic. Industrial exposure occurred mainly in the dial painting industry although we have also studied several chemists who worked at extraction and purification of radium. The principal route of entry into the body in the dial painters and chemists was ingestion, along with a smaller possibility of inhalation. In the latter case, most of the inhaled particles would have passed through the gastrointestinal tract by the clearing action of the tracheobronchial cilia.

Some idea of the size of the industrial population available for study can be obtained from the biennial issues of the city directory for the town in Illinois where radium dial painting principally occurred. Since these directories noted occupations it was a simple matter to compile lists of employees of radium dial "studios." There were 72 employees in 1924, 75 in 1926, 76 in 1928 and 36 in 1930. In addition to these city directory lists, we have 24 additional names derived from a photograph of employees taken in front of the factory building in 1924. Other towns where radium dial painting took place have been similarly investigated. Lists such as these along with photographs have enabled us to identify and trace former dial painters and to arrive at an estimate of the total population at risk. By these means, we have acquired the names of approximately 250 individuals who worked at radium dial painting in Illinois before 1930. Of these persons who were exposed to radium occupationally, we have studied 185 by whole-body gamma-ray spectroscopy and by skeletal radiography. We have examined only a few of the 200 or so persons who started to work after 1930 since all those that have been measured have small radium burdens.

The iatrogenic group of cases resulted from the administration of radium orally or by intravenous or intramuscular injections up to 1933 for treatment of a variety of diseases. These ailments included, among others, general malaise and fatigue, myocarditis, arthritis, poliomyelitis, venereal disease and mental disorders.[1,2] In some cases in our series, including children, radium was given orally as a tonic. Many of the patients were unaware that they had acquired radium, and it was only as a result of the suspicions of knowledgeable physicians that they were discovered actually to bear a radium burden. One series of at least 41 patients was treated in this way from 1931 to 1933 in a state mental hospital not far from Chicago.[3] We have studied or have other pertinent knowledge of 36 of these cases found by a deliberate search of records. In addition, we have accumulated another series of 36 patients who received radium from personal physicians. Many of these cases have come to our attention because of pathological changes that they developed, and they represent a very small sample out of the several thousand persons presumed to have been so treated by their doctors.

Theoretical Considerations

If these studies are to shed any light on the problem of maximum permissible body burdens of radium, and if the malignant tumor experience

is to be used as the principal criterion for evaluating operational safety, then a suitable method of expressing radium burden must be selected for this purpose. Whole-body counting techniques involving gamma-ray spectroscopy have made possible the rather exact measurement of radium in the human body down to levels approaching 0.001 μCi. However, delight in these recent determinations should not obscure the fact that they have been made 25 to 45 yr after the radium deposit was acquired. During this period the radium burden has followed a pattern of decreasing retention that has been shown to be mathematically describable in fairly simple terms by a power function.[4,5] Experiments with large populations of mice have led to the suggestion that the initial, or maximum, burden may be more important in evaluating tumor production by internally deposited radionuclides than any other index or measurement.[6] For this reason we have attempted in this paper and elsewhere[7,8] to evaluate the disease experience of our patients in terms of a retrospective estimate of maximum radium burden.

The calculations of these estimates have been based on the power function and its applications to the varying modes of intake of radium. The single exponential function may provide a better description for radium retention over the more recent portion of the time span than does the power function, but it cannot be used to estimate the initial or maximum body burden except in the case of a single injection.[7] Any estimate of initial body burden computed on the basis of sums of exponentials presupposes a knowledge of the parameters of early exponential curves, a knowledge that is, in fact, nonexistent.

After a single intravenous injection, retention of radium according to the power function proposed by Norris, et al.[4,5] is given by

$$R_{inj}(t) = a\, t^{b}, \quad (t \geq 1) \tag{1}$$

where t = time after administration, a is a constant that provides the intercept at unit time, and b has a negative value and is the slope of the straight line given by the function on a double-log grid. Norris, et al. proposed power function parameters of a = 0.54 and b = -0.52 for radium retention, and these values for a and b have been widely used. More recently,[7] we have re-examined the question after further investigation involving several additional radium measurements of the same state mental hospital patients whom Norris had studied. On the basis of our more recent analysis we have arrived at somewhat different mean power function values: a = 0.30, b = -0.44. This average power function was based on an arithmetic mean of the slopes and a geometric mean of the intercepts of individually determined, best fitting power functions for 8 patients for whom appropriate data were available.[7] In this series, the patient who held on to radium most tenaciously had a power function given by a = 0.18, b = -0.22, while the patient who lost radium most rapidly had values of a = 0.89, b = -0.63.

Where radium is acquired orally, as in the case of the dial painters, the amount of radium retained at t days after cessation of unit daily absorption during F days can be shown to be given by

$$R_{oral}(F,t) = \frac{a}{b+1}\left[(t+F)^{b+1} - t^{b+1}\right]. \qquad (2)$$

Figure 1 illustrates the pattern of radium retention after cessation of ingestion given by Eq. (2) and the new power function parameters for a number of selected ingestion periods. When F = 1 day, the retention curve after 90 days becomes identical with the familiar power function straight line on a log-log plot that holds for a single intravenous injection. As the ingestion period becomes longer, the earlier portion of the retention curve becomes flatter. At longer times after the end of the ingestion period, the slopes of the curves begin to approach that for a single injection.

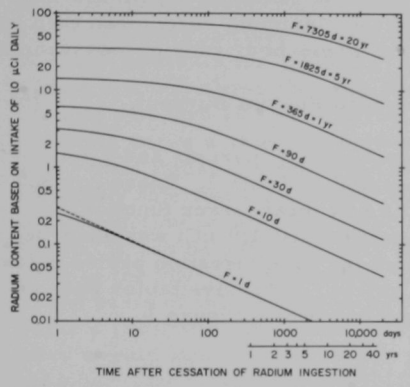

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Fig. 1. Log-log plot of radium retention after cessation of oral ingestion for ingestion periods (F) of selected lengths of time. Daily absorption of 1.0 μCi is arbitrarily assumed. Power function parameters: a = 0.30, b = -0.44.

The experimental support for this mathematical formulation was reported at the Second International Congress on Radiation Research.[9] The power function parameters for retention after a single intravenous injection in mice were shown to hold for retention after radium feeding periods of varying length. This correspondence of data supports the assumption that ingestion over a period of days can be considered to be the equivalent of the integral of a series of daily intravenous injections over the same period. In this paper this assumption, which was verified experimentally with mice, will be applied to man in order to evaulate the human experience that involved two basic routes of administration.

The point of maximum retention, which occurs at the end of the feeding period, F, is given by

$$R_{oral}(F, 0) = \frac{a}{b+1} F^{b+1}. \qquad (3)$$

In this equation the end of the ingestion period marks the beginning of the time period after cessation of administration, i.e., t = 0. The notation used here differs slightly from that of Norris[5] but the mathematical formulation is the same.

For each case where radium was acquired orally, we computed a ratio, Q, in which the radium burden at the end of the ingestion period was divided by the radium at time, t, after cessation of ingestion:

$$Q = \frac{R_{oral}(F,0)}{R_{oral}(F,t)}. \qquad (4)$$

This quotient represents the ratio of the maximum radium burden to any measured burden at time t thereafter and hence provides the factor by which the maximum burden was greater than the subsequently measured amount. For any individual measurement the maximum burden can then be estimated from the magnitude of Q and the whole-body radium measurement:

$$\text{Estimated Maximum} = Q \times (\text{Measured Radium Burden})_t. \qquad (5)$$

Sample retention values for a selected number of F periods and t intervals after cessation of ingestion are presented in Table 1. These computations are based on the parameters of the new mean power function, a = 0.30 and b = -0.44, and on the assumption that 1.0 μCi was absorbed into the body each day. The second column for each ingestion period gives the Q ratios, which are dimension-free values. Extensive tables such as these were also used to generate the curves shown in Figure 1.

TABLE 1

Values of retained radium (R) and ratio (Q) computed for t days after cessation of periods of ingestion F days in length*

Days after cessation of ingestion	Length of ingestion period (F), days									
	1		30		183		365		1825	
	R	Q	R	Q	R	Q	R	Q	R	Q
0	0.536	1.00	3.598	1.00	9.906	1.00	14.58	1.00	35.91	1.00
1	0.254	2.11	3.129	1.15	9.401	1.05	14.07	1.04	35.39	1.01
2	0.201	2.66	2.941	1.22	9.177	1.08	13.84	1.05	35.14	1.02
3	0.173	3.09	2.804	1.28	9.006	1.10	13.66	1.07	34.95	1.03
7	0.124	4.33	2.454	1.47	8.524	1.16	13.14	1.11	34.40	1.04
30	0.0667	8.03	1.707	2.11	7.187	1.38	11.64	1.25	32.64	1.10
100	0.0394	13.58	1.118	3.22	5.583	1.77	9.64	1.51	29.94	1.20
350	0.0228	23.52	0.671	5.36	3.783	2.62	7.01	2.08	25.38	1.42
1,000	0.0144	37.32	0.428	8.41	2.530	3.92	4.88	2.99	20.23	1.78
3,500	0.0083	64.71	0.248	14.52	1.497	6.62	2.95	4.94	13.70	2.62
10,000	0.0052	102.76	0.156	23.02	0.950	10.42	1.89	7.72	9.16	3.92
15,000	0.0044	122.76	0.131	27.52	0.796	12.44	1.58	9.21	7.76	4.63
20,000	0.0038	139.36	0.115	31.22	0.702	14.11	1.40	10.44	6.88	5.22

*Daily absorption of 1.0 μCi assumed. Power function parameters: a = 0.30, b = -0.44.

For the radium dial painters whose work history was known, the length of the ingestion period, F, was computed in days on the assumption that ingestion occurred throughout the period at the same rate because of

consistency in personal work habits. This computation does not correct for absence from work on weekends, holidays and vacations but is nevertheless a reasonable approximation. In the cases of those dial painters whose work history straddled January 1, 1926, we have ignored any work period subsequent to that date on the assumption that the bulk of the ingestion occurred before the practice of pointing the brushes between the lips was discontinued.

In the cases where radium was acquired medically by multiple injections, another approach was used to compute the maximum burden. Since these injections were typically given at weekly intervals, computer programs were devised to sum individual power function retention curves at 7-day intervals for $\underline{n}$ number of injections. A typical curve is given by Figure 2 which shows the step-like increase in body burden with each succeeding standard 10-μCi injection, as well as the changing shape of the retention curve with each successive injection when plotted on a log-log grid. This figure also depicts the retention of radium after a series of 15 weekly injections when such retention is described by the new average power function parameters. For cases where the number of injections is known, or can be surmised with reasonable certainty from the known practices of the physicians involved, the maximum body burden can be estimated on the basis of the number of injections and the power function parameters. Table 2 illustrates the retention values computed for selected time periods after weekly injections of 10 μCi radium for a selected number of injection periods. The radium burden obviously reaches a maximum with the final 10-μCi injection in any series of injections. The parameters for the average power function ($\underline{a}$ = 0.30, $\underline{b}$ = -0.44) were used for all the retrospective estimates reported here, except as otherwise noted.

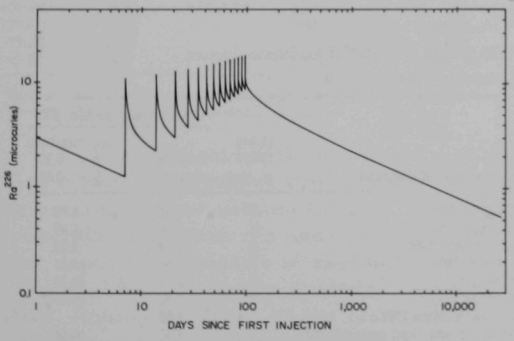

Fig. 2

Log-log plot of radium body burden during and after 15 weekly injections of 10 µCi each calculated in accordance with a newly derived power function, $R = 0.30\ t^{-0.44}$

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TABLE 2

Values of retained radium computed for t days after n weekly injections of 10 μCi*

Days after last injection	Number of weekly injections							
	1	5	10	15	20	25	30	40
0	10.000	13.691	16.435	18.579	20.415	22.052	23.548	26.237
1	3.000	6.564	9.282	11.415	13.244	14.876	16.369	19.053
2	2.211	5.664	8.357	10.479	12.301	13.929	15.418	18.097
3	1.850	5.204	7.873	9.984	11.799	13.423	14.908	17.582
7	1.274	4.319	6.897	8.966	10.756	12.362	13.833	16.489
30	0.671	2.886	5.090	6.961	8.623	10.136	11.538	14.091
100	0.395	1.871	3.532	5.046	6.447	7.760	9.000	11.306
350	0.227	1.120	2.196	3.232	4.234	5.205	6.147	7.957
1,000	0.143	0.713	1.416	2.109	2.792	3.466	4.132	5.437
3,500	0.082	0.412	0.824	1.233	1.641	2.047	2.451	3.254
10,000	0.052	0.260	0.520	0.780	1.039	1.298	1.557	2.072
15,000	0.043	0.217	0.435	0.653	0.870	1.087	1.304	1.737
20,000	0.038	0.192	0.384	0.575	0.767	0.958	1.150	1.532

*Power function parameters: a = 0.30, b = -0.44.

Malignant Tumors in Dial Painters

The malignant tumor experience among the dial painters up to September 1967 is presented in Tables 3 through 6. These tables identify the patients by code number and where known give the year of birth, work period, pathological diagnosis, date of death, the most recent radium body burden and the estimated maximum burden based on the mean power function with a = 0.30 and b = -0.44. In all, 41 patients developed 44 malignant tumors or fatal blood dyscrasias.

Table 3 lists 13 cases of malignant tumors primarily in skeletal tissues. Radium burden data are known for 8 of these cases. While the

TABLE 3

Malignant tumors in radium dial painters as a result of occupational exposure.

Tumors principally of skeletal tissues

Case No.	Year of birth	Work period	Diagnosis and year of diagnosis	Living (1967) or dead	Radium body burden, μCi	
					Current or preterminal	Est. maximum a = 0.30 b = -0.44
03-455	1906	7/22-8/23	Fibrosarcoma, left radius 1935	L	0.81	6.72
03-402*	1905	7/23-7/26	Fibrosarcoma, left femur 1954	L	1.06	6.99
03-649†	1906	10/24-10/50	Fibrosarcoma, right ischium 1954	D	1.30	8.89
03-619	1903	8/22-4/23	Fibrosarcoma, left femur 1962	D	1.50	16.14
03-401	1900	6/23-4/25	Fibrosarcoma, left leg 1963	D	2.29	15.38
03-671	1906	7/22-9/22	Fibrosarcoma, left femur 1953	D	3.82	66.49
03-584	-	-	Osteogenic sarcoma, right pelvis 1958	D	6.00	-
03-648†*	1903	9/21-9/22	Fibrosarcomas, left femur and right humerus 1956	D	7.61	63.64
03-660	1907	-	Spindle-cell sarcoma, neck 1936	D	Not studied	-
03-661	1906	-	Generalized sarcoma 1934	D	Not studied	-
03-665	1909	-	Sarcoma, retroperitoneal lymph glands 1930	D	Not studied	-
03-680	1906	-	Osteogenic sarcoma, left humerus 1946	D	Not studied	-
03-800	1909	-	Osteogenic sarcoma, left femur 1945	D	Not studied	-

*Each of these two cases also had malignant tumor of mastoid; see Table 4.
†Case 03-649 also listed as 01-023 (M.I.T. series).
†Case 03-648 also listed as 01-013 (M.I.T. series).

current or preterminal radium burdens range from 0.81 to 7.61 μCi, the estimated maximum burdens range from 6.72 to 66.49 μCi. Five cases were not studied, and the information for these persons is largely derived from death certificates. Case 03-665 may actually have had lymphosarcoma rather than a bone sarcoma, and the location of the primary tumor is not known for case 03-661.

Table 4 lists a series of tumors that are mostly cancers of epithelial or mesenchymal origin developing in an unusual set of locations: the mastoid air cells of the temporal bone of the skull, the paranasal sinuses, or at the apices of the teeth. Malignant tumors in these locations are extremely unusual, and it is noteworthy that in this series of 8 patients, deaths from these tumors have all occurred since 1953, and 6 of them were after 1960. The late appearance of these tumors is in contrast to the situation with malignant tumors of bone, which have occurred in this series from 1935 to 1963. Current or preterminal radium body burdens for the patients in Table 4 range from 0.13 to 7.61 μCi, and the estimated maximum burdens range from 1.23 to 63.64 μCi.

TABLE 4

Malignant tumors in radium dial painters as a result of occupational exposure.

Tumors principally of mastoids and paranasal sinuses

Case No.	Year of birth	Work period	Diagnosis and year of diagnosis	Living (1967) or dead	Radium body burden, μCi: Current or preterminal	Radium body burden, μCi: Est. maximum a = 0.30 b = 0.44
03-685	1902	10/21-1/23	Carcinoma, maxilla 1962	L	0.13	1.23
03-417	1909	7/24-9/25	Carcinoma, right gingiva 1962	D	0.62	5.72
03-402*	1905	7/23-7/26	Carcinoma, right mastoid 1964	L	1.06	6.99
03-407	1905	6/23-6/46	Carcinoma, right mastoid 1959	D	1.40	7.67
03-648†*	1903	9/21-9/22	Mixed carcinosarcoma, right mastoid 1955	D	7.61	63.64
03-675	1896	-	Rhabdomyosarcoma, right maxilla 1960	D	Not studied	-
03-772	1904	-	Carcinoma, left mastoid 1953	D	Not studied	-
03-785	1903	-	Carcinoma, right mastoid 1955	D	Not studied	-

*Each of these two cases also had a malignant tumor of bone; see Table 3.
†Case 03-648 also listed as 01-013 (M.I.T. series).

The situation with leukemias and other serious blood dyscrasias is less clear. Only two of the patients listed in Table 5 have had quantitative determinations of radium burden. Case 03-487 had chronic lymphatic leukemia, a disease not usually attributed to the presence of radionuclides that deposit principally in skeletal tissue. The estimated maximum for case 03-657 is based on a whole-body determination of radium burden by Prof. Robley D. Evans at the Massachusetts Institute of Technology in 1936,[10] and it is included here because this patient worked as a dial painter in the group that we have been studying, and was present in both the 1925 and 1935 pictures referred to at the beginning of this paper. Information for the other cases, again, is largely derived from hospital records, death certificates or examination of the original blood smears, and no

radium burden data are available. Two hundred and fifty women of this series painted watch dials in the 1920's. The elapsed time since ingestion of radium is 40 years. The natural incidence of myeloid leukemia in the general population is approximately one case per 16,000 subject years. In this instance, namely 10,000 subject years, the probability of seeing at least one case of myeloid leukemia in any group of 250 women observed for 40 years is high.

TABLE 5

Blood dyscrasias in radium dial painters.

Leukemias and aplastic anemias

Case No.	Year of birth	Work period	Diagnosis and year of diagnosis	Living (1967) or dead	Radium body burden, μCi: Current or preterminal	Radium body burden, μCi: Est. maximum a = 0.30 b = -0.44
03-487	1907	7/24-7/37	Chronic lymphatic leukemia 1964	D	0.37	2.57
03-657*	1906	7/22-7/36	Splenic leukemia 1939	D	18.00	55.64
03-659†	1908	-	Splenic leukemia 1934	D	Not studied	-
03-662	1901	-	Aplastic anemia 1946	D	Not studied	-
03-658	1907	-	Aplastic anemia 1938	D	Not studied	-

*Case 03-657 also listed as 01-002 (M.I.T. series). Terminal diagnosis was taken from death certificate. Body burden determination by R. Evans.[10]

†Case 03-659 died in 1938. The original blood slide made on 11/28/34 was located, and the diagnosis of chronic myeloid leukemia (formerly called "splenic leukemia") was confirmed from examination of this slide.

Finally, the malignant tumors that are <u>not</u> directly attributable at the present time to occupational exposure or to radium deposition are listed in Table 6. Current or preterminal body burdens in this series range from <0.001 to 0.90 μCi, while the corresponding estimated maximum radium burdens range from 0.20 to 7.29 μCi.

TABLE 6

Tumors in radium dial painters <u>not</u> attributed to occupational exposure

Case No.	Year of birth	Work period	Diagnosis and year of death	Living (1967) or dead	Radium body burden, μCi: Current or preterminal	Radium body burden, μCi: Est. maximum a = 0.30 b = -0.44
03-476	1895	10/27-11/27	Carcinoma of uterus	L	< 0.001	0.020
03-682	1907	-	Carcinoma of breast	L	< 0.001	-
03-403	1915	3/35-9/43	Carcinoma of ovary 1964	D	0.008	0.019
03-507	1907	6/23-8/23	Acoustic neuroma 1962	D	0.012	0.26
03-420	1906	9/22-10/26	Carcinoma of colon 1960	D	0.018	0.088
03-547	1907	7/23-8/25	Carcinoma of colon 1962	D	0.019	0.12
03-456	1921	7/43-7/51	Carcinoma of breast 1965	D	0.033	0.066
03-627	1905	7/24-7/28	Carcinoma of breast 1966	D	0.072	0.52
03-489	1911	10/26-3/28	Carcinoma of stomach 1964	D	0.12	0.84
03-408	1908	8/24-4/26	Glioblastoma 1959	D	0.16	1.13
03-499	1906	6/24-7/25	Carcinoma of thyroid	L	0.23	2.04
09-003	1892	-	Carcinoma of lung* 1963	D	0.43	-
03-586	1908	1/26-8/27	Carcinoma of breast	L	0.90	7.29
03-654	1905	-	Glioma of brain 1954	D	Not studied	-
03-667	1877	-	Carcinoma of rectum 1927	D	Not studied	-
03-815	1904	-	Carcinoma of breast 1955	D	Not studied	-

*Case 09-003 (radium chemist), who was the only male in this series, had two independent primary malignant lung tumors; the only male in Tables 3 through 6.

Malignant Tumors after Medical Administration of Radium

State Hospital Patients

This group of cases derives from a study carried out by Schlundt and his colleagues in 1931-1933 in which a group of psychotic patients at one of the state hospitals in Illinois was given weekly injections of 10 μCi of radium.[3,4] As far as we can ascertain from somewhat discrepant records, the number of injections for 30 patients ranged from 7 to 45. We have been unable to find injection data for an additional 11 patients. Most of the patients received radium when they were young adults: 25 of 33 known cases were younger than age 34, while 8 cases formed an older group with ages ranging from 47 to 63. The median age for the 33 younger cases was 27 years. Twelve patients are still alive and have been measured for radium burden and studied by periodic skeletal radiography within the past few years. In addition, 7 of the 9 patients who have died since 1955 have been similarly studied.

The mortality experience for the group of 41 patients is presented in Table 7. The details of 4 cases of malignant tumors ascribable to radium are given in Table 8. Preterminal radium burdens varied from 0.85 to 3.09 μCi, while the maximum burdens computed with the average power function parameters used in this paper ranged from 16.90 to 26.49 μCi. Similar ranges were found for all categories of mortality experience in this group. This finding suggests that there may be a minimum burden for the development of radium-induced malignant tumors but that burdens above an apparent threshold value do not guarantee the development of such tumors. It is interesting that 3 of the 4 tumors were malignancies of the skull and that, despite the large amounts of radium injected, these tumors did not develop until the last 10 years. The 3 malignant tumors that were presumably unrelated to radium were carcinomas of the bladder in 2 cases and a carcinoma of the stomach.

TABLE 7

Mortality among state hospital patients who received radium injections in 1931-1933

Clinical data (1967)	Total No. cases: Males	Total No. cases: Females	No. studied	Range of body burdens, μCi: Current or preterminal	Range of body burdens, μCi: Est. maximum $\underline{a}$ = 0.30 $\underline{b}$ = -0.44	Not studied
Malignant tumors due to radium	2	2	4	0.85-3.09	16.90-26.49	0
Malignant tumors not attributed to radium	0	3	2	0.63-1.04	14.90-24.93	1
Dead from nonmalignant disease	7	6	8	0.42-9.70	15.95-25.73	5
Dead from unknown causes	5	4	2	1.90-4.20	16.44-18.97	7
Living	3	9	12	0.44-1.40	15.95-27.77	0
Total	17	24	28			13

TABLE 8

Malignant tumors attributed to radium in state hospital patients

Case No.	Sex	Year of birth	No. of injections	Diagnosis	Year of diagnosis and death	Radium body burden, μCi	
						Preterminal	Est. maximum*
03-105	M	1904	16	Cancer (type not known) ethmoid or sphenoid sinus	1957	0.85†	18.97
03-141	M	1906	11	Carcinoma, left mastoid	1963	0.87	16.90
03-126	F	1911	20	Carcinoma, sphenoid sinus	1965	1.50‡	20.42
03-118	F	1898	41	Osteogenic sarcoma, right tibia	1955	3.09	26.49

*Estimated maximum based on average power function and number of injections.
†Computed value on basis of number of injections and elapsed time. The whole-body measurement was 2.59 μCi in 1951.
‡Corrected for missing leg by adding 15% of measured burden.

Radium Treatments by Private Physicians

A total of 37 miscellaneous patients who acquired radium from their personal physicians has come to our attention and study. Among these 37 persons, 5 males and 11 females have developed malignant tumors or blood dyscrasias that may be attributed to the presence of radium in their bodies. Since these cases were acquired principally because of the symptoms that they presented and not as a result of an epidemiological survey, the data are biased in favor of deaths from malignant tumors ascribable to radium.

The pertinent data for the 16 patients with malignancies are given in Table 9. There are 9 cases of malignant bone tumors, 5 cases of carcinoma (4 of which involve mastoids and sinuses), 1 of aplastic anemia and 1 of panmyelosis. Preterminal radium burdens ranged from 0.60 to 10.7 μCi. Estimation of the maximum radium burdens was more difficult for this series of cases and involved a variety of computations. Where the administration was oral (cases 03-208 and 03-212), the computation was based on Eq. (4) and was the same as that used for the dial painters. Where the radium was given by injection and where the number of injections was known or could be reasonably assumed, the maximum burden was estimated by the method used for the state hospital patients. The last column in Table 9 gives the number of injections assumed for each calculation and parenthetically includes the value expected by these computations for the year of the preterminal measurement (cf. Table 2).

Where estimates can be made, the maximum radium burdens range from 13.69 to 29.46 μCi for the bone tumor cases and from 17.34 to 22.05 μCi for the carcinomas of the mastoids and sinuses. Much higher estimates are obtained for the two cases of blood dyscrasia; 52.48 to 101.42 μCi. Unfortunately, comparable estimates cannot be made at the present time for the cases of blood dyscrasia among the dial painters.

TABLE 9

Malignancies and blood dyscrasias attributable to radium in other medical cases

Case No.	Sex	Diagnosis and year of diagnosis	Living (1967) or year of death	Ra administration		Last radium measurement		Estimated maximum burden	
				Year	Route	Year	μCi	μCi	Method of estimation
03-216	F	Osteogenic sarcoma, left femur 1959	1961	1922	Injections	1961	0.60	17.77	Assume 13 injections (→0.58 in 1961)*
03-227	F	Osteogenic sarcoma, right tibia 1949	1952	?	Not known	1951	0.86	-	-
03-234	F	Fibrosarcoma, right femur 1964	1965	?	Not known	1965	0.92	-	-
03-209	M	Fibrosarcoma, right scapula 1958	1960	1925-1936	Not known	1951	1.00	-	-
03-212	F	Fibrosarcoma, right tarsal scaphoid 1951	1951	1929	Oral	1951	1.30	29.46	Assume 25 days' ingestion (Q = 22.658)
03-210	M	Osteogenic sarcoma, left calcaneus 1956	1958	1926	"A few" injections	1958	1.35	13.69	Assume 5 injections (→0.29 in 1958)*
								22.05	Assume 25 injections (→1.21 in 1958)*
03-201	F	Osteogenic sarcoma, right humerus 1962	1963	?	Not known	1962	2.99	-	-
03-215	M	Fibrosarcoma, right ulna 1957	L	1920-30	Not known	1961	3.45	-	-
03-213	F	Fibrosarcoma, lumbosacral spine 1954	1955	1925-26	Several injections	1952	6.57	14.32	Assume 6 weekly injections (→0.31 in 1952)*
								20.17	Assume 6 daily injections (→0.31 in 1952)*
03-221	M	Carcinoma of oral cavity 1962	1963	1924	Injections	1957	0.62	17.77	Assume 13 injections (→0.62 in 1957)*
03-235	F	Carcinoma, sphenoid sinus 1965	L	?	Not known	1965	1.15	20.42	Assume 20 injections in 1925 (→1.00 in 1965)*
								22.05	Assume 25 injections in 1925 (→1.24 in 1965)*
03-214	F	Carcinoma, left mastoid 1959	1966	?	Not known	1964	1.23	-	-
03-232	F	Carcinoma, left mastoid 1956	1957	1917	Not known	1956	4.70	17.34	Assume 12 injections (→0.52 in 1956)*
03-240	F	Carcinoma, left mastoid 1952	1955	1920-1930	Not known	-	-	-	-
03-208†	F	Panmyelosis 1951	1953	1918	Oral	1941	10.5	75.21	Assume 12 months' ingestion (Q = 7,162)
								101.42	Assume 6 months' ingestion (Q = 9,659)
03-226	M	Aplastic anemia 1949	1953	1924	40 injections, 20 μCi weekly	1951	10.7	52.48	On basis of 40 injections, 20 μCi weekly (→4.28 in 1951)*

*Values in parentheses preceded by arrow are computed estimates of recent body burdens based on the stated assumptions and the mean power function. In some cases the correspondence between the computed and the observed burdens is very close; in other cases there is a large discrepancy.
†Case 03-208 also listed as 01-004 (M.I.T. series). Body burden determination by R. Evans.[10]

External Radiation Dose to Dial Painters

Apart from the radiation delivered to potential tumor-forming cells from radium deposited in the skeleton, some consideration should be given to the external irradiation that the dial painters might have received. In order to evaluate the magnitude of this dose, we investigated the work practices of the major dial painting plant in our territory. The physical arrangement of the desks used by the dial painters was reconstructed from photographs taken in 1922-1925 within the "radium art studios." The distances between desks have been estimated from a measurement of the width of windows, heat registers, floor boards, etc. that are shown in the photographs and that still exist in these rooms. Each dial painter sat at a wood school desk, which had a drawer under the seat that pulled out to the right, and these desks were arranged in rows from the front to the back of the room. The front edge of each desk was usually very close to the back rest of the desk in front of it so that the painters were about 80 cm apart, midline to midline. The rows were about 1 meter apart from center to center.

In order to ensure that the employees placed about the same amount of material on each of the dials painted during the day, the management issued only enough material at any one time to paint a single tray of dials. Although the radium-phosphor ratio of the material varied with the size of the dial, the number of dials in the tray and the amount of material placed on the dial also varied in such a manner that about the same amount of radium was used to paint a single tray of dials of any size. The tray of dials was placed on the open drawer adjacent to the girl's right hip and the container of radium was placed on the desk. She painted one dial at a time on the desk before her and then returned the finished dial to the tray. During the dial painting operations, the full quantity of radium was gradually transferred from the desk top to the tray alongside the right hip of the employee.

We have been reliably assured that no mesothorium or radiothorium was mixed with the radium in the companies whose employees we have studied. In fact, we have been told that the radium dial company guaranteed to the watch manufacturers that the dials contained only pure radium. To comply with this guarantee no mesothorium or even reclaimed radium was used. Of all of our cases studied by total-body counting only 2 showed evidence of contamination with ^{228}Ra (MsTh). We have ascertained that between 20 and 40 μCi of ^{226}Ra were given to each girl for one tray of dials. If we assume the most serious situation in which 40 μCi of radium were always present on the desk, and that the ^{226}Ra was in equilibrium with its daughters (which, in fact, it would not be since a significant fraction of the radon would have escaped), and that the 40 μCi of radium were located 25 cm from the anterior chest of the dial painter, then this quantity would yield an air dose to the front surface of the body of 0.6 mR/hr and about 0.3 mR/hr at the center of the chest. The 40 μCi of radium located about 35 cm behind the employee would yield a dose of about 0.3 mR/hr to her back and 0.2 mR/hr to the midline of the body. The dishes of ^{226}Ra located on the two desks immediately across the aisle and the two across the aisle diagonally behind the dial painter would give her a surface dose on each side of about 0.04 mR/hr and a midline dose of about 0.12 mR/hr (0.03×4 dishes). The radium sources on the desk in front of the worker and on the desks across the aisles one seat forward are ignored here since they were shielded by the persons seated at those desks.

The dial painters who worked surrounded by other painters, then, received as a maximum a front surface dose of about 0.6 mR/hr, a back surface dose of about 0.3 mR/hr, and a midline dose of about 0.62 mR/hr. If the painters worked 48 hr/week, 50 weeks/yr, they received a maximum of about 1.5 R/yr, a value considerably below the 5 R/yr currently accepted as permissible. If each painter had 100 μCi on her desk, the external radiation dose would not have exceeded 4 R/yr or 80 R in 20 yr.

In these calculations, the beta-ray dose has been ignored. The fact that the gamma-ray dose was based on an equilibrium mixture of ^{226}Ra, RaB and RaC rather than the appropriate mixture should more than compensate for the omission of the beta-ray dose. This reconstruction of the external dose under the work conditions of our dial painters suggests that in this series of cases the external radiation can be safely ignored as an oncogenic agent.

Discussion

The principal interest in the malignant tumor experience in the radium cases that we have been examining lies in the implications that the data may have for radiation carcinogenesis, for oncogenic dose-response curves, and for the problem of maximum permissible levels for internally deposited bone-seeking radionuclides. By relating the occurrence of a malignant tumor to an estimate of the maximum burden in each case, we have sought to avoid problems resulting from biological variability in time of appearance of tumors and variations in body burdens that result from vagaries in the time of measurement.

The results of the computations set forth in Tables 1 through 9 are summarized in Table 10 in which the estimated maximum burdens range from 6.72 to 66.49 μCi for the bone sarcoma cases, from 1.23 to 63.64 μCi for the radium-induced skull carcinoma cases, and 52.48 to 101.42 μCi for the leukemias and other blood dyscrasias (excluding the one case of chronic lymphatic leukemia, a disease which at present is not considered to be radiation-induced in man). That these estimates are lower than the values

TABLE 10

Summary of data on malignant tumors and blood dyscrasias attributable to radium deposition

Type of tumor	No. of cases	No. studied	Source of radium	Range of measured preterminal radium burdens, μCi	Range of estimated maximum burdens,* μCi
Osteo- and other sarcomas, probably arising in skeletal tissues	13	8	Occupational	0.81-7.61	6.72-66.49
	1	1	State hospital	3.09	26.49
	9	9	Other medical	0.60-6.57	13.69-29.44
Malignant tumors of the skull	8	5	Occupational	0.13-7.61	1.23-63.64
	3	3	State hospital	0.85-1.50	16.90-20.42
	5	4	Other medical	0.62-4.70	17.34-22.05
Leukemias and other blood dyscrasias	5	2	Occupational	0.37†-18.00	2.57†-55.64
	0	0	State hospital	-	-
	2	2	Other medical	10.50-10.70	52.48-101.42
Total	46	34			

*Based on power function parameters $\underline{a} = 0.30$, $\underline{b} = -0.44$.
†Case of chronic lymphatic leukemia.

yielded by Norris' parameters can be seen in Table 11, which gives comparable estimates based on other power function parameters. The retrospective estimates based on Norris' parameters are somewhat larger, but both sets are much smaller than the rather extravagant values computed by Hems[11] who lumped all the cases together and assumed that orally acquired burdens in the dial painters can be treated as if the radium had been received as a single intravenous injection 36 years earlier. Table 11 also gives the range of maximum burdens computed with the parameters for the patient in our state hospital series who retained radium most avidly ($\underline{a}$ = 0.18, $\underline{b}$ = -0.22) and with the parameters for the patient who lost radium most rapidly ($\underline{a}$ = 0.89, $\underline{b}$ = -0.63). These computations are included in order to emphasize the range of metabolic disparities that exists among the state hospital patients we have studied and that undoubtedly existed among the dial painters and other patients. While we have relied principally on the parameters of an average power function, the range of possible departures from this average function should also be kept in mind.

TABLE 11

Range of estimated maximum radium burdens computed by various power function parameters

Type of tumor	No. of cases	$\underline{a}$ = 0.30 $\underline{b}$ = -0.44	$\underline{a}$ = 0.54 $\underline{b}$ = -0.52	$\underline{a}$ = 0.18 $\underline{b}$ = -0.22	$\underline{a}$ = 0.89 $\underline{b}$ = -0.63
Osteo- and other sarcomas probably arising in skeletal tissues	12	6.72-66.49	10.11-117.36	2.28-35.84	17.35-262.96
Malignant tumors of the skull	11	1.23-63.64	1.91-98.32	0.42-35.84	3.58-184.30
Leukemias and other blood dyscrasias	4	2.57*-101.42	3.85*-160.84	0.94*-70.66	6.92*-203.87

*Case of chronic lymphatic leukemia.

The incidence of radium-induced malignant tumors in the population studied is given in Tables 12 and 13. The data for the 156 dial painters and

TABLE 12

Incidence of radium-induced malignant tumors and blood dyscrasias on basis of current and preterminal radium body burdens

(September 1967)

Current or preterminal burden	Range of estimated maximum burdens	No. of persons	Bone tumors	Other cancers	Leukemias and other blood dyscrasias	Total	Incidence
0.01-0.0316	0.019-0.48	61	0	0	0	0	0.000
0.032-0.099	0.066-17.34	30	0	0	0	0	0.000
0.10-0.316	0.11-17.34	34	0	1	0	1	0.029
0.32-0.99	1.92-24.93	37	4	3	1*	7	0.189
1.00-3.16	6.29-65.74	36	9	6	0	15	0.417
3.2-9.99	15.95-66.49	15	5	2	0	7	0.467
10.0-31.62	52.48-101.42	5	0	0	3	3	0.600
	Total	218	18	12	3	33	

*Case of chronic lymphatic leukemia not included in the radium-induced tumor incidence rate.

TABLE 13

Incidence of radium-induced malignant tumors and blood dyscrasias on basis of estimated maximum radium body burdens

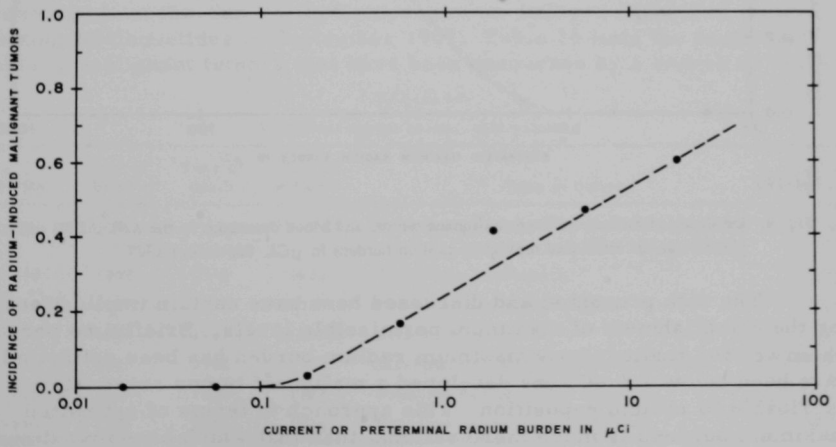
(September 1967)

Estimated maximum burdens	No. of persons	Bone tumors	Other cancers	Leukemias and other blood dyscrasias	Total	Incidence
0.01-0.0316	6	0	0	0	0	0.000
0.032-0.099	16	0	0	0	0	0.000
0.10-0.316	37	0	0	0	0	0.000
0.32-0.99	35	0	0	0	0	0.000
1.00-3.16	33	0	1	1*	1	0.030
3.2-9.99	24	3	3	0	6	0.250
10.0-31.62	47	7	6	0	13	0.277
32.0-99.9	6	2	1	2	5	0.833
100.0-316.2	1	0	0	1	1	1.000
Total	205	12	11	3	26	

*Case of chronic lymphatic leukemia not included in the radium-induced tumor incidence rate.

the 26 state hospital patients are only slightly biased since most of these cases were acquired as a result of systematic search. The medical treatment cases frequently came to our attention because of serious symptoms and to that extent they do bias the incidence data. This bias is mostly at the higher body burden levels.

The data in Table 12, which are arranged in increasing blocks of current or preterminal radium burdens, are plotted as a dose-response curve on a semilog grid in Figure 3. Except for the 0.42 incidence between

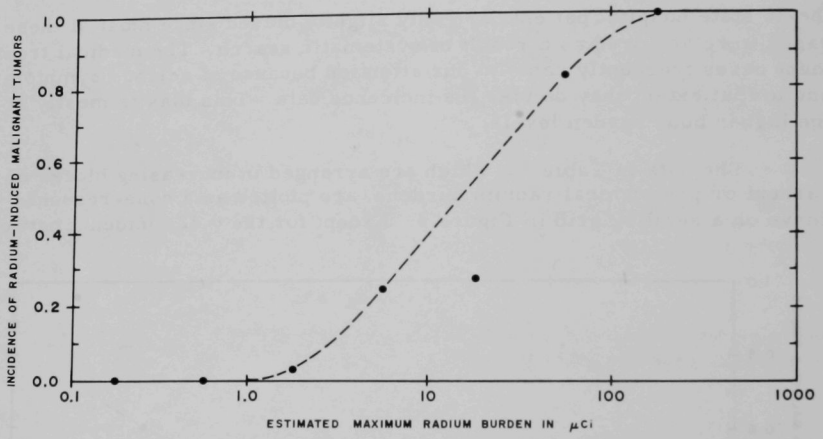


194-121

Fig. 3. Incidence of radium-induced malignant tumors and blood dyscrasias in the ANL-ACRH series plotted against current or preterminal radium burdens in μCi, September 1967

1.0 and 3.2 μCi, the other points above 0.1 μCi can be connected by a straight line or perhaps somewhat better by a slightly S-shaped curve. In either case the points above 3.2 μCi are based on rather small numbers of cases and are probably not very dependable, especially since the higher radium burdens in some cases are the consequence of measurements made 15 to 30 years ago, whereas the majority of cases were studied in the past 10 years.

More important for the establishment of a dose-response curve is the rearrangement of the 205 suitable cases in terms of blocks of increasing estimated maximum radium burdens (Table 13). Twelve fewer cases are listed here than in Table 12 because retrospective estimates of maximum burden could not be made for these dozen patients who, nevertheless, did have current or preterminal radium measurements. These data provide the dose-response curve shown on a semilog plot in Figure 4 where an S-shaped nature is more clearly evident and where a straight line is more difficult to justify.



194-120

Fig. 4. Incidence of radium-induced malignant tumors and blood dyscrasias in the ANL-ACRH series plotted against estimated maximum radium burdens in μCi, September 1967

The data presented and discussed here have certain implications for the establishment of maximum permissible levels. Briefly, no person whom we have studied whose maximum radium burden has been estimated to have been below 1.2 μCi has developed a malignant tumor reasonably ascribable to radium deposition. This approach in terms of estimated maximum burdens is much more rational than that which bases maximum permissible levels on the relationship of pathological changes to current measurements, which are high shortly after administration of the radium

and which decline steadily thereafter. The 1.2 μCi value given above and in Table 10 implies that, on the average, based on the estimated peak radium burden there is at least a twelvefold margin of safety in the currently accepted maximum permissible level of 0.1 μCi for pure ^{226}Ra and its daughters. A peak burden of 0.1 μCi would be expected to decline throughout the life of the bearer at a rate that depends on the route of administration, the amount incorporated, the time period during which the burden was acquired, and the particular bone turnover rate of the individual.

Finally, no attempt has been made here to interpret the data in terms of delivered dose. The present state of knowledge of tumor induction does not permit the delineation of the precise volume of tissue that needs to be considered as irradiated and as the site of malignant transformation. Another difficulty is in the establishment of the time span required for the induction of the malignant tumor, i.e., from the administration of the radiation to the onset of irreversible neoplastic change. This period of time, which is the real latent period and which has up to now defied even rough definition, is far more important in radiation carcinogenesis than the apparent latent period to the time of detection of the tumor or to time of death as a result of the tumor. Until these many factors involved in dosimetry and in the instigation of malignant change are resolved, the practice of computing any type of cumulative radiation dose that results in neoplasia is probably misleading and does little to illuminate the problem of radiation oncogenesis.

Appendix

Two additional tables are appended to the preceding paper since its presentation at the Sun Valley Symposium on Delayed Effects of Bone-Seeking Radionuclides in September 1967. Table 14 lists the additional cases of malignant tumors that have been uncovered by a search of records

TABLE 14

Additional tumor cases: dial painters

Case No.	Year of birth	Year of death	Worked with Ra	Type of tumor	Radium burden
03-429	1908	L	1923-27	Osteosarcoma, right third metacarpal, 1967	1.7 μCi (1966)
03-749	1902	1949	1922	Carcinoma of stomach	NS*
03-760	1907	1946	1925	Probable mastoid carcinoma	NS
03-768	1906	1964	1924-25	Astrocytoma	NS
03-779	1905	1942	1922	Sarcoma, probable fibrosarcoma, thigh	NS
03-806	1896	1956	1924	Probable sarcoma, left femur	NS
03-848	1903	1958	1918	Probable sarcoma, right femur	NS

*Not studied.

since September 1967, along with a new case of osteosarcoma involving the right third metacarpal that developed late in 1967 in one of the radium dial painters whom we have been following.

Table 15 is a preliminary analysis of the known malignant tumor experience of dial painters who worked with radium before 1930 in the Chicago area. The tumors are listed by general type, and the expected number of tumors has been computed from crude U.S. rates for white females in 1959 for specific tumor groups. While analysis of these data will have to be accomplished by use of more refined demographic techniques, the preliminary results indicate that the incidence of osteosarcomas and fibrosarcomas, of carcinomas of the mastoids and paranasal sinuses, and possibly also of central nervous system tumors is significantly greater in this group of dial painters than in the general population.

TABLE 15

Known malignant tumor experience of dial painters who worked with radium before 1930

Type of tumor	Observed tumors	Expected tumors*	Ratio O/E
Osteosarcomas and fibrosarcomas	17	0.07	243
Carcinomas of mastoids, sinuses, etc.	9	0.02	450
Central nervous system tumors	4	0.2	20
Gastrointestinal tract tumors	5	3.8	1.3
Carcinomas of breast	4	2.1	1.9
Carcinoma of lung	1	0.2	5.0

*Based on (1) known work population of approximately 200, average elapsed time about 40 years: 200×40 years = 8000 man years; (2) crude U.S. rates for white females in 1959 for specific tumor groups.

References

1. H. H. Barker and H. Schlundt. The detection, estimation and elimination of radium in living persons given radium chloride internally. II. Am. J. Roentgenol. 24, 418-423 (1930).

2. W. B. Looney, R. J. Hasterlik, A. M. Brues, and E. Skirmont. A clinical investigation of the chronic effects of radium salts administered therapeutically (1915-1931). Am. J. Roentgenol. 73, 1006-1037 (1955).

3. H. Schlundt, J. T. Nerancy, and J. P. Morris. The detection and estimation of radium in living persons. IV. The retention of soluble radium salts administered intravenously. Am. J. Roentgenol. 30, 515-522 (1933).

4. W. P. Norris, T. W. Speckman, and P. F. Gustafson. Studies of the metabolism of radium in man. Am. J. Roentgenol. 73, 785-802 (1955).

5. W. P. Norris, S. A. Tyler, and A. M. Brues. Retention of radioactive bone-seekers. Science 128, 456-462 (1958).

6. M. P. Finkel, P. B. Jinkins, and B. O. Biskis. Parameters of radiation dosage that influence production of osteogenic sarcomas in mice. Natl. Cancer Inst. Monograph No. 14, 243-270 (1964).

7. C. E. Miller and A. J. Finkel. A re-examination of retention patterns in patients who received radium by multiple injections 33 years earlier. Argonne National Laboratory Health Division Gamma-Ray Spectroscopy Group Annual Report, July 1964 through June 1965. ANL-7217, pp. 7-90.

8. A. J. Finkel, C. E. Miller, and R. J. Hasterlik. Correlation between retrospective estimates of maximum radium body burdens and clinical findings in dial painters 40 years later. Third Intern. Congr. of Radiation Research, Book of Abstracts. Cortina d'Ampezzo, Italy, 1966, p. 84.

9. A. J. Finkel and C. E. Miller. Patterns of radium retention in mice as related to man. Second Intern. Congr. of Radiation Research, Abstracts of Papers. Harrogate, England, 1962, p. 213.

10. J. C. Aub, R. D. Evans, L. H. Hempelmann, and H. S. Martland. The late effects of internally-deposited radioactive materials in man. Medicine 31, 221-329 (1952).

11. G. Hems. The risk of bone cancer in man from internally deposited radium. Brit. J. Radiol. 40, 506-511 (1967).

RETENTION OF ^{226}Ra BY CHINCHILLAS

Charles E. Miller

This study of radium retention by the chinchilla was done as a result of the suggestion by Mays[1] that the retention pattern of ^{226}Ra in the chinchilla might be closer to that in man than is that in other species such as the mouse or dog. One 3-month-old chinchilla and one 2-yr-old adult chinchilla were given ^{226}Ra by injection, and the Ra body content of these animals was measured with a gamma-ray spectrometer approximately 200 times during a period of about 500 days. These data have been analyzed extensively with the aid of an electronic computer to determine whether the retention of ^{226}Ra by the chinchilla is, in fact, different from that in the mouse but similar to that in the human.

Method of ^{226}Ra Administration

Considerable difficulty was encountered in the administration of $RaCl_2$ to the chinchillas before satisfactory results were obtained. The $RaCl_2$ was injected into the intraperitoneal cavity of one animal, which was then measured about every half hour for the next 15 hr and numerous times during the following day. The body content of Ra did not decrease during this time nor did that of the RaB-RaC daughters drop to the low value expected. On the basis of the results of a study of Ra in mice,[2] it was anticipated that the RaB-RaC content would have decreased to a minimum of about 0.25% of the injected ^{226}Ra at 400 min, after which it would have increased slowly. In order to investigate this anomaly, a 1/2-in. wide slit collimated scanner was set up, and transverse slices of the animal were scanned from head to tail. This animal was rejected when it was found that the ^{226}Ra was located in a small deposit in the abdominal cavity. Another chinchilla was given an ear vein injection of about 0.5 μCi of ^{226}Ra from a stock solution that had been prepared several years earlier. However, again the RaB-RaC daughters did not decrease as expected although most of the ^{226}Ra was lost over a few weeks. A scan of this animal also disclosed a small localized deposit in the abdomen.

A new supply of $RaCl_2$ in a saline solution was procured, and this was then successfully injected into several additional chinchillas by means of a procedure suggested by Dr. Glen N. Taylor, University of Utah.* Measurements of the distribution of Ra along the bodies of these animals with a slit scanner disclosed no large localized deposits of ^{226}Ra. Several of these animals were sacrificed to calibrate the whole-body counter, and retention patterns for two other chinchillas are reported here.

*The animal was held head downward and hot compresses applied to the ear to dilate the veins before injection.

Counting Procedure

A thin-walled, plastic bottle, 9.3 cm in diameter by 14 cm long, was fashioned into a chinchilla holder. The animal was inserted into this holder with its head located at the neck end of the bottle so that air could be pumped up along the body, past the nose, out through the cap and exhausted outside the whole-body counter. This air flow insured that radon daughter products, RaB-RaC, did not build up on the animal's fur or within the whole-body counter. A perforated, machined Lucite disk served as the bottom of the holder, both to permit air to enter and to facilitate handling of the chinchilla. A screen in the neck of the holder insured that the animal's nose was not drawn into the vacuum line attached to the bottle cap (see Figure 5).

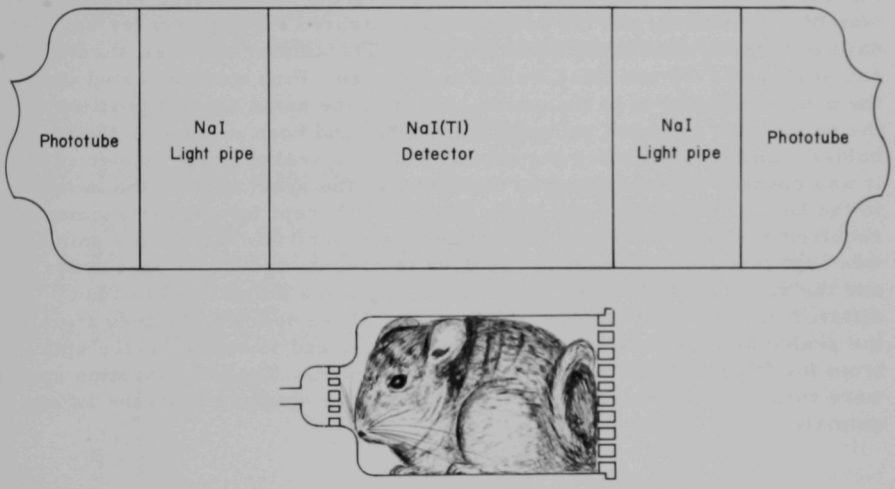


Fig. 5. Diagram of counting arrangement with chinchilla in plastic holder positioned under a 6-in. diameter by 8-in. long sodium iodide, thallium activated, log-shaped crystal

Each chinchilla was placed in the holder and counted while positioned 40 cm beneath a log-shaped sodium idodide, thallium activated crystal, 6 in. in diameter by 8 in. long, with a photomultiplier connected to each end. The axes of the crystal and the animal were parallel so that gamma rays from the animal struck the curved side of the crystal. The output of the crystal was sorted and accumulated with a 400-channel pulse-height analyzer.

The holder was positioned so that its axis was 33.7 cm from the near surface of the crystal for the measurements made during the first 34 days after injection. After 34 days considerable variability was observed in the data because of the extremely low amounts of ^{226}Ra then present in the animal. The amount of ^{226}Ra administered and counting

distances had been selected on the basis of the count rates and retentions previously found for mice, which retained 50% of the injected dose after 2 yr. To obtain more statistically accurate data the chinchilla holder was raised so that its axis was only 8.8 cm from the surface of the crystal. To provide comparison data between the two positions, measurements were made at both distances from the 34th to the 52nd days and then only at the 8.8 cm position thereafter.

Calibration

The whole-body counter was calibrated in the same manner as in a previous study of Ra retention in mice.[2] $RaCl_2$ was injected into the ear vein of a chinchilla, and the animal was measured repetitively for several days to obtain statistically accurate data. The animal was then sacrificed and sealed in a 10-mil thick walled copper can. Pins were inserted through the body and soldered to the can to hold it in the same upright position in the copper can as it had occupied when alive and been counted in the plastic holder. Immediately after the animal had been sealed in the copper can, it was counted several times to confirm that the spectra from the animal in the holder and copper can were identical. Except for the few moments required each day to record the gamma-ray spectrum, the sealed animal was kept in a dry-ice chest for 30 days to provide assurance that radon and the resultant RaB-RaC were frozen within the animal and had not diffused into the space around the animal. These spectra obtained from the sealed animal at different times were analyzed to obtain (1) the spectrum for ^{226}Ra and (2) the spectrum for RaB-RaC. These calibration spectra were then used to analyze the numerous spectra obtained from the living animals.

Results

The retention patterns for ^{226}Ra in the 3-month-old and 2-yr-old chinchillas are so different that they will be discussed separately. The 3-month-old animal was measured 30 times during the first 850 min after injection, 10 times between 1377 and 1793 min, then twice daily, then daily, and finally weekly. The values for the young chinchilla remained approximately constant during the first 445 min, dropped to 77% of the injected amount between the 445th and 536th min, to 51.8% by the 849th min, and then to 38% by the 1377th min after injection. Interestingly, the ^{226}Ra content remained constant at 38% during this first day after injection (1377 to 1793 min) and then dropped to 28% by the second day after injection (2748 min).

The excreta were collected from the cages at different times during this period and the feces separated from the wood-chip bedding that had

absorbed the urine. The feces were found to contain over 95% of the Ra eliminated, with a fecal-to-urine ratio similar to that reported for humans[3] and considerably different from that found for dogs or other animals. These measurements also demonstrated that most of the Ra was excreted during the night when the animal was active. Consequently, the ten unchanged ^{226}Ra whole-body values found between 1377 and 1793 min do not necessarily imply a constant amount in the skeleton--or skeleton plus soft tissue--but reflect only the fact that the total-body content was constant since the animal had not eliminated any feces during this period. Likewise, the constant whole-body content found during the first 445 min after injection does not necessarily represent ^{226}Ra present in the body tissue but rather the sum of this component plus that in the gastrointestinal tract. Since Ra is apparently temporarily stored in the gastrointestinal tract and eliminated at night, these data obtained between 0 to 445 min and between 1377 and 1793 min should not be used to determine the early skeletal elimination pattern.

Curve Fitting

Power Function Fit to the Data

When plotted on a log-log grid (Figure 6) the Ra retention data for the 3-month-old chinchilla from 2748 min (1.9 days) through 101,099 min (70 days) follow a slightly curved line of increasingly negative slope with time. The ^{226}Ra content, which drops rapidly between 70 and 101 days, can be fitted fairly well with a power function, $^{226}Ra = 0.50\ t^{-0.46}$ from

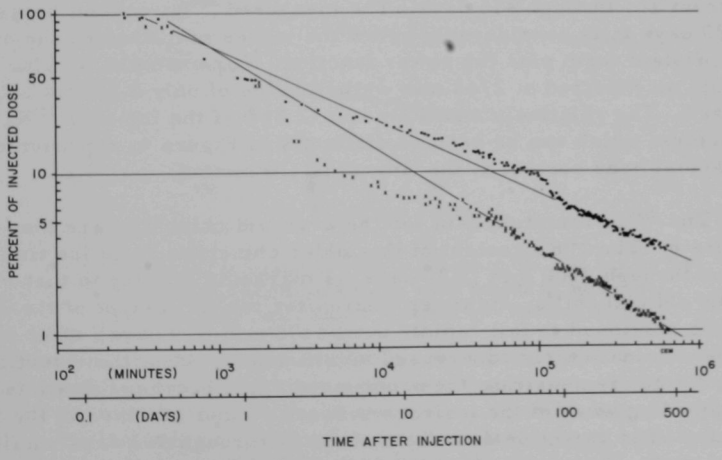


Fig. 6. Double log plot of retention of ^{226}Ra by two chinchillas. The data for the 3-month-old chinchilla are given by ● and the data for the 2-year-old chinchilla by x. Data expressed as percentage of amount injected.

101 through 416 days. The ^{226}Ra body content of the chinchilla injected at 3 months of age has remained essentially constant from the 416th day through the 500th day. This observation suggests that the retention pattern changed at about 416 days. If the retention has shifted to a new power function that is much less steep, the retention in the animal will have to be followed for several years before the magnitudes of the parameters of this recent segment can be determined.

As with ^{154}Eu retention in the chinchilla,[4] the significant drop in body content between the 70th and 101st days reflects the fact that about 2% of the injected Ra was deposited in the roots of the incisors. This volume of tooth, which grew out during the following 70 days, was worn away and eliminated between the 70th and 101st days.

Because of the relatively large variability in the measurements between 2 and 70 days, no direct attempt was made to use the computer to fit these data with the sum of a power function and a step function. However, the quantity of Ra expected in the body at the time of each of the measurements made between the 2nd and 70th days was calculated as if the retention had followed the power function found to fit the data from 101 through 436 days. When the differences between these calculated and observed values were plotted on a linear graph, these difference values from the 20th to 70th days were found to be about 2.05%. Consequently, the retention of Ra in the 3-month-old chinchilla can be considered to follow the sum of a step function (constant value) of 0.0205 plus the power function $0.50\ t^{-0.455}$ from 20 through 70 days, and then this same power function alone from 101 through 416 days. The measured ^{226}Ra content between 2 and 20 days falls considerably below the values predicted by the sum of the constant term plus the power function. For example, a value of 0.4 would be expected at 2748 min while a value of only 0.28 was actually measured. The relatively small amount (2.05% of the injected ^{226}Ra) in the incisors, which can be seen so distinctly in Figure 6, represents 20% of the actual body content at the time it is eliminated.

The ^{226}Ra retention data for the 2-yr-old chinchilla are also given in Figure 6. The ^{226}Ra content of this older chinchilla from the time of injection through 1800 min (1.25 days) is markedly similar to that in the 3-month-old chinchilla. However, thereafter the Ra content of the 2-yr-old chinchilla continued to fall rapidly until 4198 min (2.9 days), after which time the elimination rate decreased significantly. Also, the retention pattern did not demonstrate the pronounced rapid decrease at a later time due to grinding away of the incisors between 70 and 101 days in the young chinchilla. The retention data from about 27 through 468 days oscillate around a power function of $^{226}Ra = 0.47\ t^{-0.63}$. As with the 3-month-old chinchilla, the Ra content measured between 3 and 27 days falls considerably below the value predicted by the power function. At 4198 min (about 3 days), a value of 0.24 would be expected based on the power function, while only 0.12 was found by measurement.

Exponential Fit to the Data

When plotted on a semilog grid (Figure 7) the ^{226}Ra body content for the 3-month-old chinchilla falls along one smooth curve from 0 to 80 days. The Ra content drops quickly between 80 and 100 days, follows an approximately straight line from 100 to 244 days, and then a less steep second straight-line segment from 244 to 440 days. The seven additional measurements obtained between the 440th and 500th days seem to fall along a line of 0 slope. The Ra body content from 105 to 244 days can be fitted fairly well with one single exponential term, $0.1612\ e^{-0.693(t/237)}$, while the data from 244 through 440 days can be fitted by a second exponential, $0.0541\ e^{-0.693(t/564.6)}$. Although these data can be fitted with a number of discontinuous terms, such terms are of little value since they cannot be used to extrapolate to the Ra body content at later times. Consequently, these Ra retention data have been analyzed extensively with the aid of an electronic computer to determine if the sum of a series of exponential terms might fit the entire span of data and, therefore, might also hold at later times.

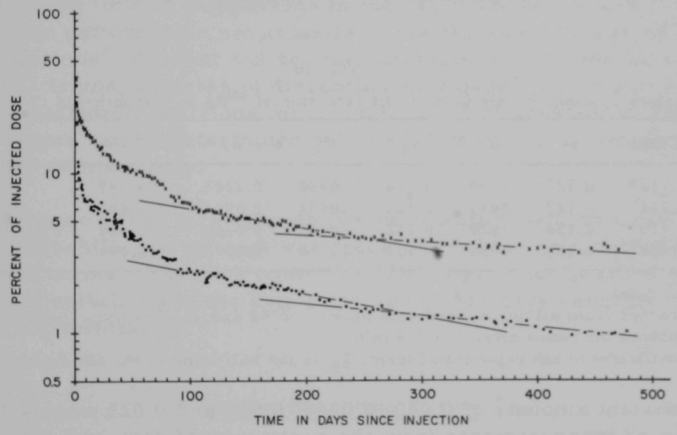


Fig. 7. Semilog plot of retention of ^{226}Ra by two chinchillas. The data for the 3-month-old chinchilla are given by x and the data for the 2-yr-old chinchilla by ●. Data expressed as percentage of amount injected.

Since no information is available concerning the true retention and elimination of Ra from the incisors, the assumption was made that the Ra content of the tooth could be considered to be a fixed Ra deposit that was passed up the incisor with time and was eliminated in toto as this volume of the tooth was ground off between the 80th and 100th days. This assumption was supported by the observation that the power function found to fit these same retention data from 100 days onward also fitted the data from 27 through 80 days if about 0.0205 (2.05%) was subtracted from each observed

value. For these exponential analyses, a constant amount was subtracted from all observed values between 0 and 80 days. This subtraction of a constant amount from all early observed total-body values does not correct for the loss of that Ra deposited throughout the volume of the tooth at the time of injection, but the amount eliminated as this volume of tooth is ground off is included as loss from the total body.

The 63 data points between 2748 min (1.9 days) and 113,714 min (78.7 days) could be fitted quite well with the sum of three exponential terms (Table 16), whose coefficients account for only 37% of the amount of ^{226}Ra injected. The remaining 63% was eliminated early and very quickly into the gut, but the parameters for this initial time period cannot be determined because of delay in the gut during daylight hours by this nocturnal animal. The ten measurements between 1377 and 1793 min were consequently omitted from the analysis. The sum of the three exponential terms predicted a value of 31.5% retention at 1377 min, while an observed value of 39.1% was found between 1377 and 1793 min. The 8% difference between the predicted and observed amounts at 1377 min might represent a quantity of Ra in the gut or it might indicate the presence of another short-term component.

TABLE 16

Parameters of exponentials found to fit retention of ^{226}Ra in 3-month-old chinchillas

Time span, min	a_1	T_1	a_2	T_2	a_3	T_3	a_4	T_4
2748 to 113,714*	0.127	1930	0.114	16332	0.1303	184,197		
2748 to 113,714†	0.127	2043	0.120	18432	0.0944	176,480		
2748 to 368,719†	0.130	1970	0.132	20116	0.0585	170,564	0.0269	4×10^{10}
2748 to 628,168†	0.130	1985	0.133	20114	0.0575	170,494	0.0274	4×10^{10}

*Normalized data.

†0.023 subtracted from all normalized data between 2748 and 113,714 min. Actual normalized values employed for times after 113,714 min.

($\underline{a}_n$ is the coefficient of nth exponential term; $\underline{T}_n$ is the half-time of the nth exponential term.)

Constant amounts of 0.020, 0.0205, 0.023 and 0.025 were subtracted from these 63 measurements from the early span of data, and the new net values combined with the 50 observed values from 146,848 through 368,719 min (102nd through 256th days). The nine observed values found between 113,714 and 146,848 min (79th through 102nd days) were omitted since the total-body Ra content did not actually drop stepwise as found with Eu.[4] When these 113 observed values were fitted with the sums of exponential terms, inspection of the fit obtained for data on either side of the break revealed that the second segment was a continuation of these early segments if about 0.023 was subtracted. The fitted values were slightly below the observed values before the break and slightly above the observed values after the break if less than 0.023 was subtracted from the early measurements. The reverse effect was observed if more than 0.023 was subtracted.

When the 63 newly adjusted early values (0.023 subtracted from observed value) were fitted with the sum of three exponentials, the parameters listed in Table 16 were obtained. The half-times of the terms agree quite well with those obtained when the actual unadjusted data were fitted.

In addition, the series of these 63 adjusted values plus the 50 values between 102 and 257 days, as well as the entire series of these 63 adjusted values plus the 79 values between 102 and 462 days, could be fitted quite well with the sum of four exponential terms given in Table 16. The half-times of the first three terms and the coefficient of the first two terms agree fairly well with the corresponding parameters of the three terms found to fit the limited span of 2748 to 113,714 min. The coefficient of the third term of the series of four is considerably less than that of a third term of the series of three since the latter term for the short span of data represents the last two terms in the four-term expression. The half-time of the fourth term (3×10^7 days) is unreasonably long. This term could be replaced by a constant value of 0.0274. This long half-time results either because of the large variability of the observed values, which span a very short period of time in comparison to the half-time of the term, or because the retention pattern does not actually follow the sum of a series of exponential functions. Whether the retention actually follows the sum of several exponential terms, a series of discontinuous exponential terms, a series of discontinuous power functions, or a combination of exponential and power function terms can be determined only by following the retention pattern for at least another year.

Because of the large variability in retention data obtained with the 2-yr-old chinchilla, no attempt was made to fit these data with the sums of exponential terms. The data from 90 to 280 days could be fitted with one single exponential, while the data from 280 to 513 days could be fitted with a second exponential.

Radon Retention Ratios

The percentage of radon produced in the body that remained in the body to decay to RaA, RaB, RaC, etc. was calculated for each measurement. Since RaA, RaB and RaC have short physical half-times, the amount of radon that remained in the body was determined by a gamma-ray measurement of the amount of RaB and RaC present. The amount of radon that would have been present if 100% had been retained was calculated by use of the equation,

$$100\% \text{ Radon Ret.} = {}^{226}\text{Ra}\left(1 - e^{-\frac{0.693}{3.825}t}\right).$$

In this equation, ^{226}Ra is the amount of Ra present at time t of the measurement in days. This formula underestimates slightly the amount of radon

produced since the value of ^{226}Ra found at time t is used as if only that amount of ^{226}Ra had been present since the time of injection. The radon produced by that Ra previously eliminated from the body is neglected. The percentage radon retained is found by dividing the observed RaB/RaC content by the calculated radon (100%) produced.

When plotted on a log-log grid (Figure 8) the percentage radon retention for the 3-month-old chinchilla varies about a straight line, % Ret. = $6.34\ t^{0.254}$, from 2 through about 200 days. The radon retention values from 208 through 513 days fall about the power function, % Ret. = $19\ t^{0.06}$. The break in the retention curve at approximately 208 days agrees with the change of slope observed in ^{226}Ra retention when plotted on a single log grid. If radon retention in the chinchilla continues to follow the second power function, a retention of 33% will be found at 29 yr, which is in good agreement with the 31.2% value actually found in humans after 29 yr[2] and the value of 30.9% predicted by extrapolation of mouse data to 29 yr.[2]

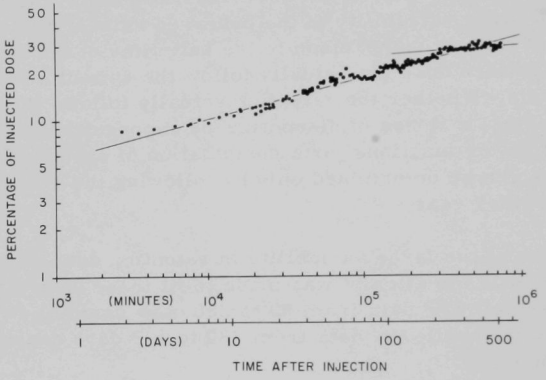


Fig. 8. Double log plot of percentage of retention of radon daughters by 3-month-old chinchilla

The percentage radon retention in the adult chinchilla falls about the power function, % Ret. = $9.68\ t^{0.169}$ from 2 through 69 days and about the power function, % Ret. = $6.60\ t^{0.239}$ from 70 through about 300 days. The radon retention values from 300 through 530 days seem to scatter about the same power function as that found for the 3-month-old chinchilla for the same time span. However, the large amount of variability present in the radon retention values because of poor counting statistics due to the small amount of Ra present in the animal and movement of the large animal within the holder prevents an accurate determination of the parameters of the power function with data from such a limited time span.

Discussion

If the hypothesis that retention of Ra in the human is similar to that in the chinchilla is true, the results of these analyses have meaningful implications. The power function, which approaches infinity as time approaches 0, has been accepted as a valid description for Ra retention after one day and has been considered to fail only during the first 24 hr.[5] So-called modified power functions, which include an appropriate exponential term, have been published that are tangential to the conventional power function at approximately one day and intercept 100% at $t = 0$. These modified power functions are assumed to be valid from time 0 onward, i.e., during the first day after injection.[5]

Retention data in the adult chinchilla from approximately 20 to 500 days can be fitted fairly well with a power function ($^{226}Ra = 0.465\ t^{-0.627}$). Similarly, retention data in the young animal can also be fitted with a power function ($^{226}Ra = 0.5\ t^{-0.455}$) from 20 through 416 days after a constant amount is subtracted from the measurements made during the first 80 days. The slopes of these two power functions are steeper than that found for humans, $^{226}Ra = 0.20\ t^{-0.36}$. For both chinchillas, the observed Ra body content at early times fell considerably below the value expected by extrapolation of the 20 to 400-day power function back to these early times.

Although retention for the first three days could not be analyzed because of the slow transit time of the Ra through the gastrointestinal tract, the observed values plus the excretion measurement suggest that only a fraction of the Ra given intravenously was actually retained in the tissues of the body. It appears that most of the injected Ra, perhaps 70% in the 3-month-old chinchilla and 80 to 90% in the 2-yr-old chinchilla, was immediately excreted into the gastrointestinal tract. Consequently, a modified power function should yield a value of approximately 0.3 instead of 1.0 at time = 0 and should become tangential to the simple power function at $t = 20$ days instead of $t = 1$ day.

The true shape of the retention curve at very early times is extremely important if late effects of Ra deposition are to be analyzed in terms of initial dose rate to the body. While the total cumulative dose to the body will not be affected by whichever modified power function is used, the dose rate to the body at day 1 may differ by a factor of 5 to 10, depending on the selection. Consequently, the shape of the retention curve during the first few days after administration is very important.

For the 3-month-old chinchilla the retention from the 2nd through the 80th day can be fitted with the sum of three exponential functions, the sum of which accounts for only 33% of the injected dose. The retention from 2 through 436 days could be fitted with the sum of these same three exponential terms plus a very long half-time term (10^7 days) that accounted for

2.7% of the injected dose. This value of 2.7% that is represented by the longest half-time is remarkably close to 2.46% of the injected dose in humans found to be eliminated by the longest half-time component (≈15 yr).[6] The extremely long half-time (10^7 days) found for the chinchilla may result because of the relatively short span of data fitted at present, which contain a fair amount of variability because of movement of the animal within the holder.

Conclusions

The retention data for intravenously administered ^{226}Ra in the chinchilla for the period from 20 to 500 days can be fitted with a power function that is similar to the Norris power function for humans, $R = 0.54\ t^{-0.52}$ (Ref. 3). However, the data from 2 through 20 days fell considerably below this power function. In fact, only 20 to 30% of the injected Ra was actually deposited in the chinchilla's body, while the remaining 70 to 80% was immediately excreted into the gastrointestinal tract and eliminated.

Recently, re-evaluation of the human data used to derive the Norris power function has demonstrated that retention of Ra in the human is best fitted with a revised power function, $R = 0.20\ t^{-0.36}$ (Ref. 6). The slope of this power function agrees with that found for dogs[7] and mice[2] but is significantly different from that found for these chinchillas. Consequently, the retention of Ra in the chinchilla is not similar to that in man, when the human data are fitted with a revised power function.

When these chinchilla data were fitted with the sum of exponentials it was found that approximately 2.7% of the injected Ra was eliminated according to a very long half-time term. This finding agrees very well with human data in that retention of Ra in humans from one year through 30 yr could be fitted by a long-term single exponential with a half-time of 15 yr that accounted for 2.46% of the injected dose. The observation that the chinchilla eliminates 70 to 80% of the Ra quite quickly is somewhat similar to the finding by Maletskos et al. when they administered short-lived ^{224}Ra to humans.[8] They found that the humans eliminated 85% of their Ra with a biological half-time of 2.4 days. Since both the human and the chinchilla eliminate about 80% of the injected dose very quickly and about 2.5% with a long half-time term, these data can be interpreted to show that retention of Ra in the chinchilla and in man in this report are similar. Furthermore, when extrapolated these chinchilla data suggest that retention of Ra in man can best be described by the sum of exponential terms.

References

1. C. W. Mays, R. D. Lloyd, G. N. Taylor, R. Stair, L. Brewster, and D. R. Atherton. Radium retention in chinchillas. Research in Radiobiology, University of Utah Report COO-119-233, September 1965, pp. 106-109.

2. C. E. Miller and A. J. Finkel. Radium retention in mice after single injection. Radiation Res. 26, 269-286 (October 1965).

3. W. P. Norris, T. W. Speckman, and P. F. Gustafson. Studies of the metabolism of radium in man. Am. J. Roentgenol. 73, 785-802 (May 1955).

4. C. E. Miller. Retention of ^{154}Eu by chinchilla and mice. This report.

5. J. H. Marshall. The modified power function model of alkaline earth metabolism. Health Phys. 12, 1161 (August 1966).

6. C. E. Miller and A. J. Finkel. Radium retention in man after multiple injections: The power function re-evaluated. Am. J. Roentgenol., in press.

7. M. Goldman, R. J. Della Rosa, and D. H. McKelvie. Metabolic, dosimetric and pathological consequences in the skeletons of beagles fed Sr^{90}. Delayed Effects of Bone-Seeking Radionuclides. University of Utah Press, Salt Lake City, Utah, in press.

8. C. J. Maletskos, A. T. Keane, N. C. Telles, and R. D. Evans. Intestinal absorption of Ra^{224} and Th^{234} and some dosimetric considerations of Ra^{224} in human beings. Delayed Effects of Bone-Seeking Radionuclides. University of Utah Press, Salt Lake City, Utah, in press.

RETENTION OF ^{154}Eu BY CHINCHILLAS AND MICE

Charles E. Miller

Retention of intravenously administered ^{154}Eu in six mice and in one adult chinchilla was measured by gamma-ray spectrometry for about 18 months. This study was undertaken (1) to determine if the retention pattern of this bone-seeking rare earth in these two species is similar to that of radium, which is an alkaline earth, (2) to compare biological half-times of ^{154}Eu in these two species with that found for ^{154}Eu in man,[1] and (3) to compare the fit to the retention data obtained by the sum of exponentials with that obtained by a power function.

Retention of ^{154}Eu by the Adult Chinchilla

Approximately 1.26 μCi of ^{154}Eu, as $EuCl_3$ in 0.15 cc of physiological saline solution, was administered by gavage to one adult 2-yr-old male chinchilla and intravenously into an ear vein of a second similar animal.

For measurement of retained ^{154}Eu, each chinchilla was placed in a thin-walled plastic holder and counted while positioned 40 cm beneath a log-shaped sodium iodide, thallium activated crystal, 6 in. in diameter by 8 in. long with a photomultiplier connected to each end. The axis of the crystal and the animal were parallel so that gamma rays from the animal struck the curved side of the crystal. The output of the crystal was sorted and accumulated with a 400-channel pulse-height analyzer.

The chinchilla that had been given ^{154}Eu intravenously was counted for 10 min, beginning 4 min after administration, and again several times during the first and second days. Starting with the third day it was counted once daily for several days and less frequently thereafter for 600 days to date. The same measurement schedule was followed for the first few days for the chinchilla that had received ^{154}Eu by gavage. During this time this chinchilla lost all of the administered Eu, and consequently data will not be given for this animal since apparently none of the Eu was absorbed from its gastrointestinal tract.

The count rate in the energy band from 515 to 1440 keV was determined for each measurement. In order to normalize the data for purposes of analysis, the count rate for each measurement was divided by the count rate found at the time of the first measurement. The retention at various times was thus expressed as a decimal fraction of the administered dose.

Single Exponential Analysis

The retention of ^{154}Eu by the adult chinchilla presents an interesting pattern. When plotted on a semilog grid (Figure 9), the data from the time of administration through 79,420 min (55 days) scatter about one curved line, the data from 90,609 min (63 days) through 521,280 min (362 days) fall along a second curved line, while the data from 531,421 min (376 days) through 859,752 min (597 days) fall along a straight-line segment.

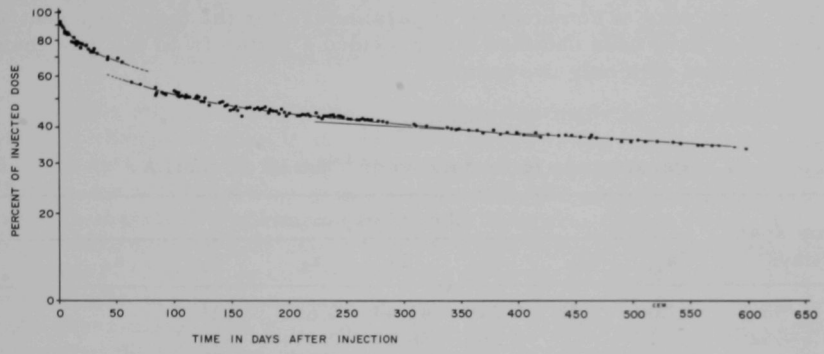


Fig. 9. Semilog plot of ^{154}Eu retention by a 2-yr-old chinchilla. Data expressed as percentage of amount injected. Discrete break between the 55th and 63rd days represents the loss of a large deposit of ^{154}Eu from the incisors.

The large stepwise drop between the 55th and 63rd days reflects the rather sudden and rapid elimination of about 10% of the amount of ^{154}Eu injected. Such a drop could occur only if either the elimination rate increased significantly for a short period of time 55 days after the ^{154}Eu was administered or if a relatively large deposit in some compartment in the body was suddenly eliminated in toto. This loss apparently occurs because a significant fraction of the administered ^{154}Eu is incorporated into the animal's incisors. As a result of continuous growth of the incisors, the Eu deposit is in effect transported along the incisors and is eliminated during the short period when the labeled portions of incisors are ground off by chewing. Very little, if any, of this ^{154}Eu is absorbed from the gastrointestinal tract.

The 33 measurements made between 1228 min and 55 days were fitted with the sum of three exponential terms, and the measurements made between 63 and 362 days were fitted with two exponential terms. Parameters of these exponential terms, which were obtained with the aid of an electronic computer, are given in Table 17. The excellent agreement between the parameters of these two exponential terms found to fit the data obtained between 63 and 362 days and the parameters of the last two exponential terms found to fit the early time span suggest that the later section of the curve is a continuation of, although about 10% below, the first curve. When

an attempt was made to fit the 88 measurements made between the 63rd and 362nd days with three exponential terms, the computer program effectively reduced the series of three terms to the identical series of two terms found when the computer was instructed to find the best fitting series of two terms (Table 17). The sum of the two coefficients was also approximately equal to the coefficient of the corresponding coefficient of the two-term series. This observation suggests that the retention from 63 through 362 days actually follows the curve described by the sum of two exponential terms. Otherwise, a combination of parameters for the three exponential terms would have been obtained that provided a better fit to the data than the fit obtained with only two terms.

TABLE 17

Parameters for retention of ^{154}Eu in chinchilla

Time span, days	Sum of exponentials*							
	a_1	T_1	a_2	T_2	a_3	T_3	a_4	T_4
1-55.1	0.109	3.42	0.249	41.44	0.602	915.7		
62.5-362			0.266	38.27	0.514	915.2		
62.5-362			0.265	38.39	0.067	915.5	0.477	917.0
369-510					0.471	1289.1		
369-597					0.471	1289.1		

Time span, days	Power functions†	
	a	b
0.85-55	0.863	0.0859
62.5-271	1.377	0.2114
280-597	1.801	0.2594

*Retention = $\sum \left(A_n e^{-0.693(t/T_n)}\right)$ where t is the time in days since injection.

†Retention = $a\, t^{-b}$.

The same results were not obtained when a larger span of data, 0 to 400 days, for example, was fitted first with the sum of two and then with the sum of three exponential terms. As additional measurements after the 362nd day became available and were added to the series, the half-times of the two exponential terms were found to increase with the number of measurements added. Furthermore, the series of three exponential terms was not reduced to two terms as before; the magnitudes of these parameters were also found to depend upon the time span employed. When a series of four terms was employed, the computer set the coefficient of one term negative to obtain the best fit. The observation that the magnitude of the

parameters depends upon the time span covered by the data proves that the computer program only converged to the parameters that provided the best fit to these data but that these parameters did not necessarily provide an exact fit to the data. Otherwise, the addition of later measurements that fell along the curve described by the series of exponential terms found to fit the early data would not have altered the parameters found to fit the larger sets of data. Proof of this statement can be found in the analyses above the data between 1228 min and 53 days and between 63 and 362 days. Curve-fitting to both sections of data yielded about the same two long half-time parameters. Of particular significance in this example is the fact that there were no common data points in the two series.

After sufficient additional measurements made at later times were plotted, a change of slope in the retention curve at 362 days could be seen. When the data from 362 through 510 days, and recently the data from 362 to 597 days, were fitted with a single exponential, the computer program converged to exactly the same parameters for both sets of data (Table 17). Most of the observed data fell within 1% of the value predicted by the single exponential and only one observed point fell as much as 2% off this line. Consequently, the retention pattern from 362 through 597 days follows a single exponential. The half-time of this term (1289.1 days) is only 40% longer than the half-time of the longest term (915.7 days) found to fit the data from 63 through 362 days, while the coefficient is almost identical.

The retention pattern of ^{154}Eu in the chinchilla can be expressed by a continuous function until 362 days and by a single exponential term from 362 to 597 days. Additional data must be obtained to determine the span covered by this term. The complete series of data from 63 through 597 days does not follow the sum of a series of exponential terms.

Power Function Analysis

The data were also plotted on a log-log grid (Figure 10). These data follow a slightly curving line from 1220 min through 55 days, exhibit the discrete break between 55 and 66 days discussed above, scatter about a straight line from 63 through 271 days and a second straight line from 278 through 587 days. When 10% was arbitrarily subtracted from each data point between 1228 and 79,413 min (55 days) to account for the step function loss from the teeth, the resultant values could be fitted within ±5% by a single power function (Table 17). That is, the measured values at each end of the time span fell 5% below the value given by the power function while the measured values in the middle of the time span were 5% above the computed values. The parameters of the power function found to fit the data between 63 and 271 days and 278 and 510 days are also given in the table. Obviously, if the retention is to be expressed as a power function, a number of power functions, each limited to a certain span of data, must be specified.

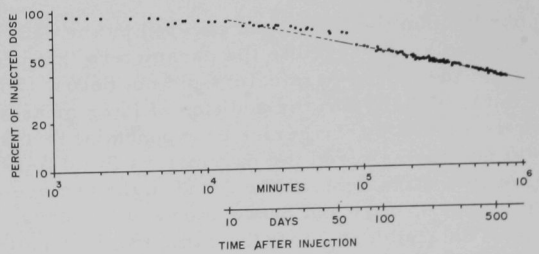


Fig. 10. Double log plot of ^{154}Eu retention by a 2-yr-old chinchilla. Data expressed as percentage of amount injected.

Discussion

The results obtained by the two analyses lead to two very different conclusions. The data from 1228 min (about 1 day) through 362 days could be fitted with the sum of three exponentials plus a step function. The data from 362 through 510 days could be fitted with a single exponential term whose half-life was only slightly greater than the longest half-time term employed to fit the data to 362 days. The entire series could only be fitted with a sum of exponential terms plus a step function if the sign of the coefficient of at least one of the terms was allowed to be negative. Consequently, this analysis suggests that retention follows one pattern for 362 days and then shifts to a new pattern.

When the power function analysis was employed the data from 1 through 55 days could be fitted approximately by one power function plus a step function to account for the tooth deposit, while the data from 63 through 271 days and from 278 through 510 days could each be fitted quite well by a single power function. This analysis suggests that the retention pattern changed between the 55th and 63rd days, and again between the 271st and 278th days, while the exponential analysis suggests that the pattern changed only once at 362 days.

Retention of ^{154}Eu by Mice

About 0.15 μCi of ^{154}Eu, as $EuCl_3$ in 0.02 cc of physiological NaCl solution, was injected into a lateral tail vein of each of six male 3-month-old CF-1 white mice. The mice were caged individually in standard mouse cages with food and water always available. They were all fed the same diet during the entire period of measurement and were housed in a temperature- and humidity-controlled laboratory to avoid the possibility that changes in the temperature might influence retention patterns. Immediately after the $^{154}EuCl_3$ was injected, each mouse was placed into a Lusteroid tube and the gamma-ray spectrum was determined from the first to the fifth minute after injection. The Lusteroid tube, which contained the mouse, was

accurately positioned with the aid of a mechanical fixture under a log-shaped sodium iodide crystal, which was 6 in. in diameter by 8 in. long. The pulses from the sodium iodide crystal were sorted and accumulated with a 400-channel pulse-height analyzer. The mice were measured several times on the day of injection, two or three times a day for several days thereafter, daily, and finally weekly. Through the 533rd day after injection, 167 measurements have been recorded.

The net count rate in the energy band from 510 keV to 1.44 MeV was obtained for each measurement and divided by the count rate obtained during the first measurement, which occurred 1 to 5 min after injection. The data on all six mice were normalized to a retention of unity at 3 min--mid-time of the first 4-min measurement--and all later retentions were given as a decimal fraction of this value.

Single Exponential Analysis

The retention data from each mouse have been fitted with exponential and power function terms to determine whether retention actually follows either one of these expressions. Considerable difficulty was encountered when an attempt was made to fit these retention data (Figure 11) with the sum of exponential terms by means of a computer. If the retention pattern truly follows the sum of a series of exponential terms, the computer program will yield the same parameters for the exponential terms regardless of the time span of data employed. It will yield parameters that are dependent upon the time span of data if (1) fewer exponentials are employed than are actually required to fit the data, or (2) the data simply do not follow the sum of any number of exponentials. In each case, the computer program converges to the best fit to the data but does not yield a true fit to the data.

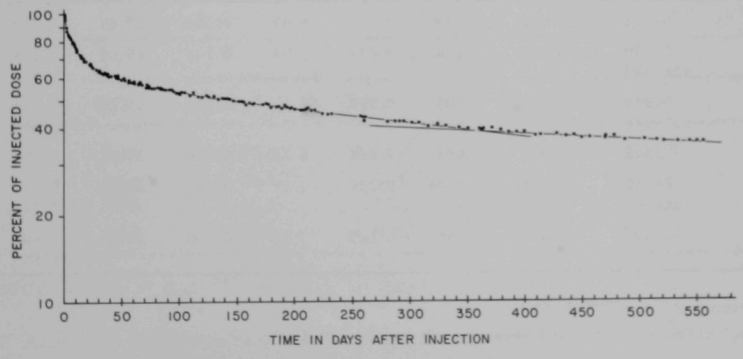


Fig. 11. Semilog plot of ^{154}Eu retention by a 3-month-old male CF-1 mouse following single intravenous injection

For each mouse any time span of data from 0 through 100 days to 0 through 330 days could be fitted quite well with the sum of four exponential terms, and the computer program yielded about the same parameters for the four exponential terms regardless of the time span of data employed (Table 18). As a result, the retention of Eu by the 3-month-old male mouse seems to follow the sum of four exponential terms from 0 to 330 days. When additional measurements made after 330 days were added to this series of measurements, the computer program converged to successively longer and longer half-times for the four exponential terms as later measurements were added. While this observation might suggest that the data should be fitted with the sum of five or six exponential terms, the parameters found when five or six terms were employed were not only still dependent upon the number of retention measurements employed but the sign of one term was negative. A negative coefficient in the sum of exponentials implies that the animal is ingesting radioactivity during the course of the study, which was an impossibility in this case. The retention measurements made between 330 and 543 days could be fitted quite well with a single exponential term (Table 18) whose half-time was approximately 40% longer than the half-time of the longest term of the series of four terms found to fit the 0 through 330-day span of data. Consequently, one of two conclusions must be drawn: (1) The metabolic pattern of ^{154}Eu in the mouse changes after 330 days due to aging of the animal, or (2) the retention of ^{154}Eu in the mouse does not follow the sum of exponential terms but should be stated by some other mathematical function.

TABLE 18

Parameters for exponential function found to fit ^{154}Eu retention in mice

Mouse No.	Time span, days	Parameters*							
		a_1	T_1	a_2	T_2	a_3	T_3	a_4	T_4
1†	0-224	0.058	0.242	0.244	6.05	0.126	27.48	0.563	680
2	0-330	0.061	0.224	0.241	7.52	0.108	29.69	0.594	570
2	324-543							0.524	882
3	0-456	0.059	0.608	0.250	9.10	0.131	65.28	0.546	816
3	435-543							0.469	1376
4†	0-228	0.014	1.098	0.244	6.71	0.116	37.21	0.607	531
5	0-330	0.024	0.410	0.224	7.58	0.147	27.69	0.611	714
5	324-543							0.584	882
6	0-330	0.074	0.410	0.189	7.92	0.130	27.83	0.604	602
6	313-543							0.507	1117

*Retention = $\sum \left(A_n e^{-0.693(t/T_n)}\right)$.

†Mouse 1 sacrificed after 224 days, mouse 4 after 228 days.

Power Function Analysis

The data, when plotted on a log-log grid, follow the pattern given in Figure 12. The data for each mouse fall along three separate discontinuous

power functions; that is, the data from 0.5 through 7 days after injection fall along one power function, the data from 7 through 145 days fall along a second power function, while the data from 145 through 553 days fall along a third power function. The parameters of the power functions and the time spans for which they are valid are given in Table 19.

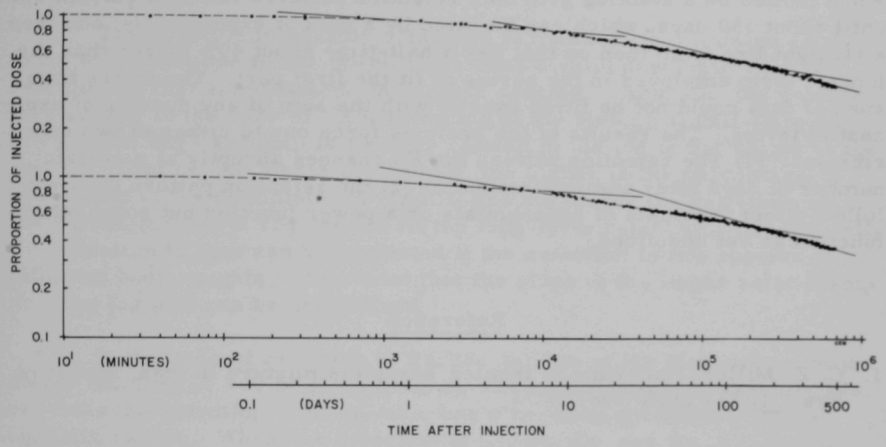


Fig. 12. Double log plot of ^{154}Eu retention in two CF-1 male mice following intravenous injection

TABLE 19

Parameters for power function analysis of ^{154}Eu in mice

Mouse No.	Time spans: 0.5-6.9 d, Parameters a_1*	b_1*	7.9-147 d, Parameters a_2	b_2	172-543 d, Parameters a_3	b_3
2	0.921	0.054	1.094	0.156	2.169	0.291
3	0.931	0.062	1.098	0.153	2.120	0.282
5	0.966	0.054	1.151	0.156	1.887	0.249
6	0.917	0.056	1.098	0.151	1.967	0.267

*Retention of Ra = $a_n t^{-b_n}$, when t is days.

Although the data can be fitted quite accurately with these discontinuous power functions, the results are of little value since each power function is valid for only a limited span of time and cannot be extrapolated to times beyond that covered by the analysis.

Conclusions

The retention patterns of Eu in mice and in chinchillas are very similar. When plotted on a log-log grid both retention curves demonstrate two distinct breaks and can be fitted by three discontinuous power functions. When plotted on a semilog grid both retention patterns follow a smooth curve until about 350 days, which can be fitted by a sum of exponentials, and then a straight line from then on that has a half-time about 40% longer than the longest term employed in the series to fit the first part. The entire time span of data could not be fitted exactly with the sum of any number of exponential terms. The results of the analysis force one to either of two conclusions: (1) The retention pattern for Eu changes abruptly at a certain number of days after administration, or (2) the retention pattern does not follow either the sums of exponentials or a power function but some other function as yet undefined.

Reference

1. C. E. Miller, Half-time of inhaled europium mixture in man. Radiation Res. 31, 541 (July 1967).

COMPARISON OF ^{154}Eu AND ^{226}Ra RETENTION BY MICE AND CHINCHILLAS

Charles E. Miller

The question invariably arises as to whether the retention expression found for an isotope in one species provides a valid description for the retention of that same isotope in another species. Langham[1] has demonstrated that in the case of $^{65}ZnCl_2$ the log of the biological half-time for mice, rats, dogs and man is linearly related to the log of the weight of the animal. That is, the larger the animal, the higher is the percentage absorption of the administered $^{65}ZnCl_2$ and the longer the half-time of the exponential term required to fit the long-term retention. Consequently, the retention in man can be predicted if the retention in two species of different body weights is known so that the slope of the linear relationship on a log log plot can be determined.

In the case of retention of Ra, the validity of the parameters of the power function, $R = 0.54\ t^{-0.52}$ (Ref. 2), although universally employed to describe the retention of Ra in man, has often been questioned for the opposite reason. While the retention of Sr, Ba, Ca, and Ra in animals, and of Sr, Ba, and Ca in man all follow power functions of similar slopes, the retention of Ra in man seemed to follow a power function of much steeper slope. A recent reanalysis of the data originally used to arrive at the power function, $0.54\ t^{-0.52}$, has led to a new power function, $0.20\ t^{-0.35}$ (Ref. 3). This new slope of -0.35 is very close to that found for dogs by Goldman[4] and slightly steeper than that found by us for mice (-0.29).[5] These results suggest that retention of Ra is either similar in mice, dogs, and humans or that the long-term retention may be inversely related to body weight.

Since the retention patterns of ^{154}Eu were obtained for mice and chinchillas with the hope that these patterns could be extrapolated to man, the retention patterns of Ra and Eu in mice were compared to those in chinchillas. If these two species demonstrated the same pattern for both Ra and Eu, perhaps the Eu retention pattern for mice and chinchilla could be extrapolated to man.

The percentages of the injected dose of ^{226}Ra and ^{154}Eu in mice and in chinchillas at different times after administration are given in Table 20. From 70 to 500 days after administration the 2-yr-old chinchillas and 3-month-old mice contained practically identical percentages of the injected dose of Eu. The chinchillas contained approximately 7 to 8% more ^{154}Eu on the 10th and 50th days than the mouse because of the Eu deposit in their incisors. If the deposit in the incisor is ignored, the retention patterns for ^{154}Eu in these two species are identical from 10 through 500 days.

TABLE 20. Percentage retention of ^{226}Ra and ^{154}Eu in mice and chinchillas of various ages at selected times after injection

	Europium		Radium		Radium	
Day	Mouse (3 mo)	Chinchilla (2 yr)	Mouse (3 mo)	Chinchilla (2 yr)	Mouse (1 mo)	Chinchilla (3 mo)
1	92	93	60.2	28.3	80.2	-
2	90	88.5	52	21	76.0	27.1
10	77	84	38.5	6.8	62	18.9
50	62	70	25.8	4.2	43	11.2
70	57	56.7	22.5	3.2	39.7	9.4
100	53	53	19.7	2.5	38.1	6.2
200	46.5	45	16.5	1.8	34.4	4.8
300	41.4	41	14.9	1.2	33.2	3.75
400	38	38.5	13.7	1.07	-	3.38
450	36.5	37	-	0.98	-	3.36
500	35.4	35.5	-	-	-	-

In order to present comparable data for Ra in these two species, the percentage of the injected Ra dose retained by a mouse that was also 3 months of age at the time of injection was compared to that retained by a chinchilla that was approximately 2 years old at the time of injection (Table 20). These data reveal that the mouse retained considerably more Ra than the chinchilla. In terms of the percentage of the injected dose at 10 days after the Ra was administered, the mouse retained 5.7 times more Ra than did the chinchilla. This ratio of (Ra in mouse/Ra in chinchilla) increased with time until at 400 days when retention by the mouse was 12.9 times that in the chinchilla (13.7 to 1.07%). Thus the larger chinchilla loses the bone-seeking Ra much more rapidly than the smaller mouse.

To prove that this effect is not (at least entirely) due to the different ages of the two animals, comparable data for a 1-month-old mouse and a 3-month-old chinchilla are also given in the table. At 10 days the 1-month-old mouse contained 3.3 times as much Ra as the chinchilla and again the ratio increased with time until at 300 days the mouse contained 8.9 times as much. Biologically, the 1-month-old and 3-month-old mice are probably equivalent to a 3-month-old and a 2-yr-old chinchilla in that the younger animals in each case are about half-grown while the older animals are young adults. Regardless of the ages of the mice and chinchillas compared, the chinchillas lost the Ra more rapidly than the mice. The significant fact here is that the two species retained approximately the same percentage of injected Eu dose but significantly different percentages of the injected dose of Ra.

The isotopes, Ra and Eu, are not in the same chemical family; Ra is grouped with Ca, Sr, and Ba, and is a bone-seeker in that in time it is distributed throughout the volume of bone. Eu, on the other hand, is a rare earth with a valence of +3, more similar to Pu, and probably deposits on the surface of the bone (i.e., a bone-surface seeker). It is interesting that two species of very different life-spans retain about the same percentage of Eu at the same number of days after injection but very different amounts of Ra.

References

1. W. H. Langham, Applications of whole-body liquid scintillation counters. Radioactivity in Man, Ed. G. R. Meneely. Charles C. Thomas, Springfield, Ill., 1961, pp. 311-322.

2. W. P. Norris, T. W. Speckman, and P. F. Gustafson. Studies of the metabolism of radium in man. Am. J. Roetgenol. 73, 785-802 (May 1955).

3. C. E. Miller and A. J. Finkel. Radium retention in man after multiple injections: The power function re-evaluated. Am. J. Roentgenol., in press.

4. M. Goldman, R. J. Della Rosa, and D. H. McKelvie. Metabolic, dosimetric and pathological consequences in the skeletons of beagles fed Sr^{90}. Delayed Effects of Bone-Seeking Radionuclides. Univ. of Utah Press, Salt Lake City, Utah, in press.

5. C. E. Miller and A. J. Finkel. Radium retention in mice after single injection. Radiation Res. 26, 269-286 (October 1965).

PRECISION OF ASSAY OF WHOLE-BODY POTASSIUM IN MAN*

Charles E. Miller, Alexander P. Remenchik,** and Wayne V. Kessler†

A controversy exists regarding the accuracy of measurement of potassium in intact, healthy humans. Some groups, principally whole-body counter specialists, maintain that K measurements are intrinsically accurate and that any daily or weekly variations in the measurements reflect changes in the amount of K in the body. Other groups maintain that the amount of K in the body remains constant and that variations of K in the same subject are due to random errors in whole-body counter measurements. As evidenced by the number of papers in the literature, a third group maintains that current whole-body measurements are inaccurate but that a variety of newly developed techniques is more accurate and reliable.

There is no simple, direct method by which the accuracy of a particular whole-body counting system may be assayed since the amount of K in a human cannot be measured directly. One direct approach would be to measure the K content of a cadaver by various whole-body counter techniques and then perform a chemical analysis for K on the complete body. However, in order to make a proper comparative analysis it would be necessary to measure and analyze chemically a large number of cadavers that ranged in weight from approximately 45 to 160 kg, since the calibration factor for a whole-body counter technique varies as some function of the person's height and weight. Obviously, a project of such scope is impractical because of time, cost, and unavailability of specimens.

Some insight into the accuracy of whole-body counter techniques may be obtained by measuring a large group of subjects for K by various methods and comparing the results. To this end, the K content of each of 44 clinically healthy subjects,†† whose weights ranged from 44 to 170 kg, was measured by either two or three whole-body counter techniques (which employed a sodium iodide crystal as the detector), with a 4-pi liquid scintillation counter, and by an isotopic dilution method. By a careful analysis of the results, some indication of the accuracy of the various techniques for measuring K has been obtained.

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††The term "subject" rather than "patient" is used to emphasize that only healthy, ambulatory persons participated in this study.

Measurement of Subjects

The normal gamma-ray spectrum of each subject was obtained first by the tilting-chair technique in the Argonne crystal whole-body counter. The subject was seated in the tilting chair within the whole-body counter, and his spectrum was obtained with each of two sodium iodide crystals located in turn over the chair.

A squat, right cylindrical, sodium iodide crystal, 8 in. in diameter by 4 in. thick (called the 8 by 4 crystal), was positioned over the chair with the crystal axis vertical.[1] When a crystal of this shape is used, the gamma rays from the subject's head strike the side of the crystal, those from the torso strike mainly the 8-in. diameter face of the crystal, and those from the legs strike either the side or the face of the crystal. Consequently, the absolute detection efficiency of the system is dependent upon the location of the radioactivity in the body, since the solid angle that is subtended from the radioactive deposit to the crystal is different for the radioactivity in various volumes of the body.

A so-called log crystal (6 in. in diameter and 8 in. long) was located over the chair with the crystal axis horizontal and parallel to the back and seat of the chair. The cross section of the crystal is the same when viewed from any point in the body. The absolute detection efficiency does depend upon the distance and mass between the radioactive deposit and the detector, but no variation is attributable to the shape of the presenting side of the detector.

Each subject was measured for 40 min with both the 8 by 4 crystal and the log crystal. Measurements, or factors calculated from measurements, made with the 8 by 4 crystal and the log crystal over the tilting chair (TC) are designated as 8 x 4 TC and log TC.

A number of the subjects were also measured in a supine position on a Lucite slab within the whole-body counter. The subject's normal gamma-ray spectrum was recorded with the 8 by 4 crystal located in turn at each of seven equally spaced locations 24.5 cm apart along the body.[1] The crystal was positioned with its axis vertical and the 8-in. diameter face of the crystal located either 30, 35.8 or 37 cm from the surface of the slab. A 30-min measurement was made at each of the seven positions for a total count time of 3.5 hr for each subject.

Unless otherwise stated in the text, the count rates from the seven crystal positions were summed, and one count rate was employed. Measurements or factors calculated from measurements based on this sum count rate are designated 7-crystal sum. This count rate would be equivalent to that obtained by a longitudinal scan of the body that required $3\frac{1}{2}$ hr or to a 30-min count with seven crystals.

The subjects were then measured in the Purdue University 4-pi liquid counter.* Three series of four 1-min measurements were made of the subject's $^{39,40}K$ (normal potassium). Two 1-min background measurements were made before and after measuring the subject and each series of four 1-min measurements. Background was thus measured for a total of eight 1-min periods, and the subject was measured for a total of twelve 1-min periods.

A carefully measured volume of ^{42}K was then given to each subject, either orally or intravenously, and two equal volumes were pipetted into standard bottles. Each subject was remeasured by each technique 2 to 5 days later, after the ^{42}K had become equilibrated with the subject's $^{39,40}K$. Very short count times were used with the crystal counters for these ^{42}K measurements since the subjects yielded relatively high count rates. All of the urine was collected from each subject between the time of ^{42}K administration and the ^{42}K measurements.

Measurement of $^{39,40}K$ and ^{42}K Standards

In order to avoid the use of the decay scheme of $^{39,40}K$ and ^{42}K, the following procedures were used: For measurement with the crystal whole-body counter, a specified amount of distilled water was added to the ^{42}K standard bottle that was then placed on a tray that had been accurately positioned with a calibrated mechanical fixture 40 cm below the crystal. Repeated measurements made previous to and during this study demonstrated that the uncertainty in ^{42}K count rates due to pipetting, ^{42}K counting statistics, and positioning of the standard bottles introduced an error of less than 1%. A known amount of KCl was placed in a bottle, which was identical in size and shape to that used for the ^{42}K standard, and it was also counted on a tray located 40 cm from the crystal. Although the ^{42}K and the $^{39,40}K$ were counted in different bottles, previous studies had demonstrated that identical spectra, i.e., count rates, were obtained from equal volumes of ^{42}K mixed in the same volumes of distilled water, KOH, or KCl.

In the Purdue 4-pi liquid counter, a known amount of KCl, dissolved in a 2-gal polyethylene bottle of distilled water, was counted on the same day that a subject's $^{39,40}K$ was measured. The ^{42}K standard, equal in volume to that given to a subject, was then mixed with the contents of this same 2-gal polyethylene bottle, which was then recounted.

All urine voided between the time of administration and each whole-body measurement was analyzed to determine the amount of ^{42}K eliminated, and each subject's ^{42}K count rate was corrected for excretion and decay to some arbitrary time, usually noon of the day of the measurement. The ^{42}K count rate from the standard bottle was also corrected for decay to this same time.

*Reference 2 describes 2-pi liquid counter, since converted to 4-pi.

The $^{42}K/^{39,40}K$ ratio present in the urine 42 to 50 hr after administration was also computed. From a knowledge of the ^{42}K content of the body and this ratio, the amount of so-called exchangeable potassium in the body could be calculated (isotope dilution technique).[3]

Analysis of Data

The data have been analyzed (1) to calculate the calibration factor for each measurement technique employed for each subject in this study, (2) to determine the dependence or lack of dependence of the calibration factor on the weight, height, etc., of the subject, (3) to calculate each subject's $^{39,40}K$ content when the calibration constant derived for his own body configuration is used, (4) to evaluate the size of the error that may exist if the average calibration factor corrected for the subject's weight is used to compute the K content of subjects who had not received ^{42}K, (5) to calculate the ratios between the exchangeable K content (found by the isotopic dilution technique) and the total-body K (found by each whole-body counter technique), (6) to determine which whole-body counter technique yields more consistent ratios for all subjects, and (7) to evaluate the variability in either isotopic dilution measurements or the exchangeable fraction in humans.

To obtain the necessary factors to perform the various analyses, the measurements were substituted into the universally used equation for calculating a human's K content:

$$\text{Grams K} = A \times \frac{B}{C} \times \frac{D}{E}, \qquad (1)$$

where

A is the count rate from subject's $^{39,40}K$,

B is grams of $^{39,40}K$ in the bottle,

C is count rate from $^{39,40}K$ in the bottle,

D is count rate for ^{42}K in the bottle,

E is count rate for ^{42}K in the subject.

The value of A varies from subject to subject since A is related to the amount of $^{39,40}K$ in the body. The product of the second and third terms is the calibration factor for the whole-body counter, and its value varies for the different subjects if the counter efficiency is dependent on body build. The magnitude of the second term is a constant if both the sensitivity of the counter and the energy calibration of the spectrometer do not change with time. In the Argonne crystal whole-body counter, measurements made with various bottles of KOH, KCl, and KF, all of which contained known

amounts of K and were accurately positioned with the aid of a mechanical fixture 40 cm from the face of the crystal, have yielded the same count rate/g of $^{39,40}K$ during the last 10 yr. The magnitude of the last term, D/E, varies from subject to subject and reflects the dependence of the calibration factor upon body build.

Since the possibility exists that the energy calibration may have been slightly different on succeeding days, only the last term, the G (geometry) factor = D/E, is analyzed to evaluate the dependence of the calibration factor on height and weight. Any variation in energy calibration should not affect the magnitude of this term since both D (^{42}K count rate from bottle) and E (^{42}K count rate from subject) were measured on the same day. In the 4-pi liquid counter, the values of A ($^{39,40}K$ count rate from subject) and C ($^{39,40}K$ count rate from standard bottle) were obtained on the same day so again small changes in counter sensitivity should have introduced equal canceling errors into these two terms and should not have affected the calculated K content of the subject.

The G factors obtained for the subject measured by each technique were fitted with a regression line of the form, $\log(G) = a + b(w)$, with the aid of an electronic computer. The logarithms of the G factors were used as the dependent variables, and the weights of the subjects in kilograms were used as the independent variables. The values and associated standard errors of a and b for the regression line found to fit the various groups of calibration factors are given in Table 21.

TABLE 21

Parameters of regression lines for G factors and for % G spread with various whole-body counter techniques

Technique	Energy band	Number of subjects		a	S.E.$_a$	b	S.E.$_b$
4-pi liquid counter	0.8-1.8 MeV	42	G factor	-0.0293	0.0093	0.001806	0.000093
			% G spread	1.4590	1.4471	0.019696	0.014584
8 x 4 tilting chair	Compton	44	G factor	0.2012	0.0075	-0.000190	0.000074
			% G spread	0.1365	1.1084	0.027403	0.010958
	Photopeak	44	G factor	0.2028	0.0083	0.000995	0.000082
			% G spread	-0.4735	1.1732	0.036115	0.011599
8 x 4 tilting chair	Compton	29	G factor	0.2011	0.0073	-0.000281	0.000093
			% G spread	2.4763	1.1034	-0.008218	0.014072
	Photopeak	29	G factor	0.2097	0.0064	0.000922	0.000081
			% G spread	1.4994	0.8071	0.003655	0.010292
Log tilting chair	Compton	18	G factor	0.0431	0.0073	-0.000054	0.000076
			% G spread	0.9831	0.9094	0.010925	0.009534
	Photopeak	18	G factor	0.2836	0.0099	0.001133	0.000103
			% G spread	1.1018	1.1852	0.017324	0.012424
Log tilting chair	Compton	23	G factor	0.1073	0.0110	-0.000405	0.000107
			% G spread	-1.1599	1.3654	0.041313	0.013206
	Photopeak	23	G factor	0.0860	0.0133	0.000834	0.000129
			% G spread	-1.2831	1.7824	0.046930	0.017241

The computer was programmed to calculate the percentage that the subject's actual G factor differed from the value predicted by the regression line for a subject of the same weight:

$$\%\ G\ \text{spread} = \frac{G\ \text{observed} - G\ \text{calculated}}{G\ \text{calculated}} \times 100. \qquad (2)$$

To avoid misunderstanding, this percentage difference [Equation (2)] is designated % G spread rather than percentage of error although it is the percentage that a subject's K content would be in error if the calculated G factor were used. The % G spread for each subject found when the G factors obtained by each technique were fitted with a regression line is given in Table 22.

TABLE 22

Percentage that subject's G factor falls above or below regression line

Subject	Height, cm	Weight, kg	4-pi liquid	8 x 4 tilting chair		Log tilting chair			
				Compton	Photopeak	Compton	Photopeak	Compton	Photopeak
1-A1	161.2	43.9	0.07	-1.71	-0.79	-1.00	-0.43	-	-
2-A2	161.2	45.2	-1.30	0.88	2.88	-	-	0.57	1.90
3-B1	154.7	48.5	2.39	0.96	1.24	-0.58	1.06	-	-
4-B2	154.7	49.7	2.51	7.42	1.92	-	-	-2.44	-0.71
5	161.4	52.7	-2.44	-2.68	-2.21	0.84	1.40	-	-
6	178.3	53.7	-0.78	3.66	1.34	-	-	1.98	1.69
7*	162.7	55.6	7.93	7.08	9.97	-	-	8.49	6.96
8	163.0	55.9	-0.20	0.64	1.01	1.22	1.79	-	-
9	167.7	56.4	-1.21	0.93	2.41	2.99	3.09	-	-
10	153.5	57.6	7.64	-4.81	-2.66	-	-	-0.37	0.73
11	163.6	57.9	1.88	1.31	1.88	-	-	1.64	3.34
12	170.4	63.3	3.33	-0.81	1.60	-	-	-1.44	-0.03
13	158.8	64.0	5.19	2.76	4.60	-	-	1.54	1.05
14	168.9	70.3	-1.27	-1.41	-1.40	-1.46	-2.33	-	-
15	179.9	71.8	-2.27	-0.50	-1.10	0.70	-1.78	-	-
16	184.2	72.9	-1.01	-0.29	-1.46	-	-	1.51	1.06
17-C3	163.6	73.7	-11.48	-0.49	1.66	0.32	-0.98	-	-
18-C2	163.6	73.7	-5.44	4.00	3.57	4.19	4.54	-	-
19	174.5	74.5	-0.64	-0.86	-2.27	-	-	0.46	-3.67
20	185.2	85.0	0.27	2.22	0.36	-	-	1.31	0.92
21	189.7	87.2	-1.70	1.04	-0.63	-	-	1.98	-1.66
22	178.1	88.4	3.66	3.16	1.40	-	-	1.91	2.81
23-C1	163.6	88.9	-0.87	0.46	2.31	-0.51	0.71	-	-
24	184.1	92.9	-4.97	-2.72	-5.11	-3.77	-7.61	-	-
25-D3	161.2	97.5	1.54	-1.13	-0.87	-2.84	-2.69	-	-
26-D2	161.2	102.3	1.70	0.40	-0.54	-4.30	-3.06	-	-
27	165.1	102.5	-2.07	-4.72	-1.67	-	-	-	-
28-E2	166.4	113.8	-8.44	1.57	1.30	2.17	3.41	-	-
29-F2	170.9	118.4	-	0.23	3.27	-	-	1.61	2.31
30-G1	165.7	119.7	1.17	-1.63	-1.47	-	-	-	-
31	160.0	120.1	1.42	-9.17	-9.03	-	-	-9.93	-9.86
32-H1	154.5	121.1	11.30	-3.56	-1.04	-	-	-4.29	-2.94
33-G2	165.7	121.1	4.88	-3.43	-7.04	-	-	-1.31	-3.83
34-H2*	154.5	121.8	1.19	4.02	14.37	-	-	7.72	11.23
35	188.1	123.3	-6.72	-8.00	-11.91	-	-	-8.41	-13.24
36-J2	178.5	125.3	2.71	-2.30	-7.38	-	-	-	-
37-D1	161.2	128.0	-1.01	0.13	0.39	-2.91	-3.42	-	-
38	170.0	128.2	8.00	3.44	4.80	-	-	2.14	4.40
39	171.0	128.9	11.76	-0.26	1.43	-	-	2.47	2.24
40-E1	166.4	130.9	-0.81	1.93	2.21	2.09	5.38	-	-
41	172.8	136.6	-1.35	-5.04	-3.12	-	-	-3.88	-0.63
42	160.5	143.1	-3.97	-3.41	-1.38	-	-	2.68	2.18
43-J1	178.5	147.8	-1.80	3.17	-0.34	0.21	-1.06	-	-
44-F1	170.9	149.6	-0.22	9.74	11.02	-	-	8.34	6.34
45	159.2	150.4	-	2.02	7.14	-	-	3.63	8.09
46	183.0	157.0	-5.11	9.94	7.45	3.14	2.96	-	-
47*	186.9	167.1	-9.47	-5.60	-15.14	-	-	-3.53	-13.08
N			42	44	44	18	18		23
Mean			3.30	2.74	2.97	1.96	2.65	2.86	3.29
S.D.M.			3.18	2.61	2.86	1.38	1.83	2.60	3.26
S.E.M.			0.49	0.39	0.43	0.32	0.43	0.54	0.68

*Not included in calculation of mean.

The absolute values of these % G spreads (Table 22) were fitted with a linear regression line, % G spread = a + b(w), to determine if the magnitude of the errors was dependent upon the subject's weight. The values and standard errors of a and b of this regression line found to fit the % G spread are given in Table 21 immediately below the parameters of the regression line found to fit the G factors.

4-pi Liquid Scintillation Whole-Body Counter

The G factors found for the 4-pi liquid counter (line 1, Table 21) are very dependent upon the weight of the subject, as demonstrated by the value of b (slope) and standard error of b. The % G spreads, while yielding a positive slope (0.0197), are not statistically dependent (standard error of slope = ±0.0146) upon the weight of the subject ($P > 0.1$). Examination of the % G spreads for the 4-pi liquid counter in column 4 of Table 22, confirms this result in that the five subjects who yielded the largest % G spread (7 to 11.8%) are not grouped at the bottom of the table with the large subjects, but are randomly distributed in the table. In the absence of a statistically significant correlation between error and weight, the mean, standard deviation of the mean, and standard error are given at the bottom of the column. A mean error of 3.3% with a standard deviation of 3.18% exists for these G factors.

8 x 4 Crystal over Tilting Chair

Since the K content of the subject is routinely calculated with the count rate from two energy bands, two calibration factors are employed. For $^{39,40}K$ measurements the first energy band (Compton band) includes the scattered gamma rays whose energies fall between 0.775 keV and 1.275 MeV, while the second energy band (photopeak band) includes mainly unscattered gamma rays whose energies fall from 1.325 and 1.575 MeV. In order to calculate the G factor for ^{42}K measurements, the same lower energy band is used for the Compton band but an energy band of 1.375 to 1.625 MeV is used for the photopeak band.

The parameters of the regression line found to fit the G factor for the Compton band are given in line 3 of Table 21; those from the photopeak band are given in line 5 of Table 21. The Compton G factors support a regression line of negative slope and the photopeak G factors support a regression line of positive slope. Both slopes are significant ($P < 0.01$).

The parameters of the regression line calculated to fit the percent errors by which the observed G factors differ from the calculated G factors are given in lines 4 and 6, Table 21. The slopes of these regression lines are significant ($P < 0.01$) and demonstrate that the spread in G factors along the regression line increases as the weight of the person increases.

Inspection of the percentage by which the observed G factors differ from the regression line given in columns 5 and 6 of Table 22 discloses that the large variations exist for subjects who weigh more than 120 kg. To insure that the G factor of the large subjects did not unduly affect the regression line calculated for the G factor for the entire series of subjects, new regression lines were calculated for the 29 subjects who weighed between 43.88 and 119.71 kg. The parameters for these regression lines (lines 7 and 9 of Table 21) are not statistically different from those found to fit the entire series of 44 subjects that included 15 subjects who weighed between 120 and 157 kg. Since approximately the same regression line was obtained, the % G spread for each of these 29 subjects was very close to those in Table 22. However, while the % G spreads for the total series of 44 subjects were related to the weights of the subjects, no correlation exists between the % G spread and the weights of these 29 subjects. The % G spreads based on the Compton data had a mean of 1.858 (S.D. of mean = 1.650, S.E. of mean = 0.306) and those based on the photopeak data yielded a mean of 1.648 (S.D. of mean = 1.189, S.E. of mean = 0.221).

Log Crystal over Tilting Chair

When the log crystal was placed in operation initially, it was positioned over the chair at an arbitrarily selected reproducible height with the aid of the mechanical fixture used to position the 8 by 4 crystal. After measuring several subjects, it was found necessary to raise the crystal 2.5 cm to accommodate several of the larger subjects. A number of subjects were subsequently measured with the log crystal at this higher position. The G factors obtained with the log crystal must, therefore, be analyzed as two groups.

The parameters of the regression lines that fit the log data for 18 subjects when the crystal was located at the closer distance are given in lines 11 and 13 of Table 21. Neither the G factor, nor the associated % G spread based on the Compton data, yields a statistically significant slope. The G factors based on the photopeak data support a significant slope ($P < 0.01$), while the % G spread does not yield a statistically significant slope.

The parameters of the regression lines found to fit the log crystal G factors for the 23 subjects measured with the crystal raised 2.5 cm are given in lines 15 and 17 of Table 21. Interestingly, both the Compton and photopeak G factors yield statistically significant slopes and intercepts. The slopes of the % G spread are also significant ($P < 0.01$).

7-Crystal Technique

When the study of potassium by the 7-crystal technique was begun, the measurements were made with the face of the crystal 30 cm above the surface of the rigid Lucite slab used as a bed. This spacing had proved

satisfactory for all studies of the distribution of ^{226}Ra, ^{137}Cs, ^{154}Eu, and other radioelements in humans. Unfortunately, in the present study it was necessary to reposition the crystal at 35.8 cm and then at 37 cm above the bed to accommodate some of the very large, obese subjects.

The sets of G factors obtained for 9 measurements with the crystal 30 cm above the bed and for 10 measurements with the crystal 35.8 cm above the bed were analyzed. In order to obtain a valid comparison with the % G spreads obtained with other counting techniques, the G factors obtained by the other methods for these same subjects were also fitted with regression lines. The parameters and their standard errors for these regression lines are given in Table 23. The % G spreads for each subject with each technique for both groups are given in Table 24.

TABLE 23

Parameters and standard errors of the parameters of the regression lines log G = a + b(w) found to fit the G factors obtained by each technique for one series of 9 subjects and another series of 10 subjects

Technique	Energy band	Number of subjects	a	$S.E._a$	b	$S.E._b$
4-pi liquid counter	0.8 to 1.8 MeV	9	-0.0036	0.0187	0.00154	0.00023
		10	-0.0621	0.0266	0.00197	0.00023
8 x 4 tilting chair	Compton	9	0.2319	0.0157	-0.00063	0.00019
		10	0.1806	0.0153	0.00007	0.00013
	Photopeak	9	0.2497	0.0124	0.00029	0.00015
		10	0.2012	0.0141	0.00107	0.00012
Log tilting chair*	Compton	9	0.1222	0.0125	0.00066	0.00015
		10	0.0392	0.0170	-0.00001	0.00014
	Photopeak	9	0.1217	0.0131	0.00024	0.00016
		10	0.0264	0.0196	0.00117	0.00017
7-crystal sum†	Compton	9	-0.6654	0.0095	0.00056	0.00012
		10	-0.5694	0.0127	0.00068	0.00011
	Photopeak	9	-0.6144	0.0058	0.00121	0.00007
		10	-0.5112	0.0118	0.00133	0.00010

*Log crystal at closer position over tilting chair for 9 subjects, farther position for 10 subjects.
†Face of 8 by 4 crystal 30 cm from bed for 9 subjects, and 35.8 cm for 10 subjects.

TABLE 24

Percentage that subject's G factor falls above or below regression line

Subject	Height, cm	Weight, kg	4-pi liquid	8 x 4 tilting chair		Log tilting chair		7-crystal sum	
				Compton	Photopeak	Compton	Photopeak	Compton	Photopeak
9 subjects with crystal 30 cm above bed									
2-A2	161.2	45.2	-4.42	-1.54	-0.58	-0.18	-0.11	-1.52	-2.21
4-B2	154.7	49.7	-0.47	5.32	-0.78	-2.90	-2.06	-0.83	0.38
10	153.5	57.6	5.01	-5.91	-4.01	-0.38	0.45	1.27	0.89
12	170.4	63.3	1.14	-1.39	1.13	-1.12	0.48	-1.18	-0.40
13	158.8	64.0	3.01	2.23	4.23	1.92	1.66	2.66	1.83
19	174.5	74.5	-2.09	-0.30	-0.93	1.46	-1.67	0.20	-0.12
21	189.7	87.2	-2.41	2.93	2.84	3.78	2.15	0.32	0.40
33-G2	165.7	121.1	6.26	1.87	1.69	2.48	4.68	-3.59	-1.57
35	188.1	123.3	-5.38	-2.74	-3.29	-4.77	-5.27	2.83	0.87
Mean			3.36	2.69	2.17	2.11	2.06	1.60	0.96
S.D. of mean			2.01	1.84	1.44	1.53	1.82	1.18	0.74
S.E. of mean			0.67	0.61	0.48	0.51	0.61	0.39	0.24
10 subjects with crystal 35.8 cm above bed									
17-C3	163.6	73.7	-7.18	-0.16	0.66	0.54	-1.18	-3.24	-2.55
18-C2	163.6	73.7	-0.84	4.34	2.55	4.42	4.34	2.71	2.04
23-C1	163.6	88.9	3.35	-0.13	1.02	-0.42	0.37	-0.13	-0.74
25-D3	161.2	97.5	5.53	-2.21	-2.27	-2.83	-3.09	-1.13	-1.40
26-D2	161.2	102.3	5.50	-0.98	-2.02	-4.34	-3.50	0.63	1.13
28-E2	166.4	113.8	-5.45	-0.52	-0.44	2.02	2.84	2.80	2.65
37-D1	161.2	128.0	1.68	-2.76	-1.57	-3.18	-4.07	-0.16	0.74
40-E1	166.4	130.9	1.77	-1.20	0.16	1.78	4.64	0.34	0.61
43-J1	178.5	147.8	0.11	-1.00	-2.64	-0.24	-1.89	-3.16	-3.26
46	182.9	157.0	-3.60	4.92	4.80	2.60	2.01	1.54	0.94
Mean			3.50	1.82	1.81	2.24	2.79	1.58	1.61
S.D. of mean			2.37	1.70	1.38	1.53	1.41	1.28	0.94
S.E. of mean			0.74	0.54	0.44	0.48	0.44	0.41	0.30

The G factors for the 7-crystal sum are highly dependent upon the weight of the subject (lines 11 through 14, Table 23). Also, the individual G factors for each subject fall very near the regression lines as evidenced by the small % G spread values given in columns 9 and 10 of Table 24.

The slopes of the regression lines found to fit the G factors for the groups of 9 subjects with the 8 x 4 TC and log TC are much less steep and completely different from the slopes found for the group of 10 subjects or for the entire series of subjects. The slopes for these two techniques were influenced unduly by the inclusion of subjects 33 and 35 in this small series of 9 subjects. The slopes of the regression lines found to fit the G factors for the two groups with the 4-pi liquid counter also are statistically different from each other but not as much as those obtained with the tilting-chair technique. The slopes of the regression lines found to fit the G factors with the 7-crystal technique are not particularly different even though the crystal was at different heights from the bed for each series. The values of a found with the 7-crystal sum for the two groups are different, a result that would be expected since the height of the crystal was 30 cm above the bed for the series of 9 subjects and 35.8 cm above the bed for the series of 10 subjects.

Appropriate statistical tests demonstrated that no significant correlation exists between the weights of the subjects and the % G spreads given in Table 24 for any of the four counting techniques. Consequently, means, S.D. of means, and S.E. of means are given at the bottom of each column. The 4-pi liquid counter G factors yielded the largest mean error while the 7-crystal sum yielded the smallest % G spread. It should be emphasized at this point that a good fit to the G factors from only 10, or even 20, subjects does not demonstrate the superiority of a technique but may reflect accidental subject selection.

Discussion of Analyses of G Factors

The parameters and associated standard errors of the regression lines calculated to fit these data denote that the G factors are highly dependent upon the subject's weight. Of great importance is the finding that the G factors obtained for some subjects are as much as 10 to 12% above or below the regression line found to fit the whole series of measurements.

Significantly, there is very little, if any, correlation between errors in G factors found by the 4-pi liquid counter and those found by the tilting-chair technique, although there is a high degree of correlation between the errors found by the two tilting-chair techniques (Table 22). For 5 subjects (10, 17, 28, 32, and 39) of the 7 whose 4-pi liquid counter G factors fell more than 6% off the calculated regression line, the G factor found with the 8 x 4 TC fell within 2.7% of the regression line for these data. The G factor for the sixth subject (38) fell 4.8% off the line, and the G factor for the seventh subject (35) was much farther from the regression line, 11.9 versus -6.72%.

On the other hand, while there is a mean difference of 1.84% between the % G spreads for the 8 by 4 crystal and % G spreads for the log crystal, those subjects (31 and 35) whose G factors fell 9 and 12% below the regression line found with the 8 by 4 crystal also fell 9.86 and 13.2% below the regression line found with the log crystal. Conversely, those subjects (44 and 45) whose G factors fell 11 and 7.1% above the 8 by 4 crystal regression line also fell 6.3 and 8.08% above the regression line found for the log crystal G factor. This agreement proves conclusively that (1) the count rate obtained with the tilting-chair technique is dependent upon the location of the ^{42}K in the body, and (2) these variations are not due to instrumentation errors.

About 1.0% of the 1.8% mean difference between the errors of columns 6 and 10, Table 22, is due to counting statistics associated with ^{42}K counts of the subjects. The addition of 0.8% must be ascribed to movement by the subject and to the varying sensitivities of the two very differently shaped crystals to distribution of ^{42}K in the body.

These data demonstrate the necessity of measuring many subjects before any claim can be made that a particular whole-body counter design yields a count rate that is independent of body build and K distribution. The G factors obtained for 18 subjects with the log crystal at the closer of the two positions did not diverge from the regression line at higher body weights as did the G factor when the crystal was at the greater distance. Consequently, these data obtained with the log crystal can be used to suggest that the G factors will fall much closer to the regression line if the closer crystal spacing is used and, therefore, the superiority of this crystal spacing is implied. However, these data when compared with the results obtained with the 8 by 4 crystal prove just the opposite. Examination of the % G spread values given for the 8 by 4 crystal, wherein all subjects were measured with the same crystal spacing, reveals that those subjects whose G factors fell farthest from the regression line for the 8 by 4 crystal G factors happened to have been measured with the log crystal when it was located at the greater distance. In fact, the G factors found for these 18 subjects with the log crystal at the closer spacing fall farther from the regression line than the G factors found for these subjects with the 8 by 4 crystal. As would be expected, placing of the crystal closer to the body increases the spread in G factor variation.

Exchangeable K Ratio

The G factor obtained from the ^{42}K measurements on each subject was used to calculate his body content of K. Each subject's body K value, measured by the isotopic dilution method, was divided by the value calculated from the whole-body counter technique and this ratio is given in percent in Table 25. The whole-body counter K values are presented in this form

because (1) the results are easier to comprehend since the values are all essentially normalized to the same base line, and (2) these ratios can be analyzed to determine the variability in the so-called exchangeable K pool of the body from subject to subject.

TABLE 25

Exchangeable K ratio calculated with subject's G factor

Subject	Height, cm	Weight, kg	4-pi liquid		8 x 4 tilting chair		7-crystal sum		Log tilting chair	
			Ratio	C.V.*	Ratio	C.V.	Ratio	C.V.	Ratio	C.V.
41	172.8	136.6	82.43	1.28	91.97	2.37	-	-	88.63	1.98
47	186.9	167.1	77.34	1.08	100.03	2.13	-	-	87.03	1.65
42	160.5	143.1	110.17	2.16	106.46	3.05	-	-	109.33	2.69
1-A1	161.2	43.9	90.96	2.00	98.38	3.92	-	-	96.65	3.16
3-B1	154.7	48.5	105.01	2.00	110.88	3.86	-	-	105.17	2.98
5	161.4	52.7	101.07	2.00	98.14	3.61	-	-	93.80	2.88
8	163.0	55.9	108.23	1.84	112.59	3.58	-	-	109.89	2.84
32-H1	154.5	121.1	107.04	1.95	92.71	3.14	-	-	92.60	2.74
27	165.1	102.5	99.09	1.38	103.58	2.64	-	-	-	-
30-G1	165.7	119.7	98.13	1.96	98.21	3.02	-	-	-	-
45	159.2	150.4	-	-	95.36	2.97	-	-	99.23	2.58
24	184.1	92.9	90.67	0.99	92.16	2.10	-	-	93.49	1.70
15	179.9	71.8	90.81	0.98	93.64	2.22	-	-	95.08	1.81
9	167.7	56.4	72.58	1.68	78.97	3.62	-	-	82.06	3.02
14	168.9	70.3	85.86	1.25	90.81	2.68	-	-	87.87	2.12
Mean			94.24		97.59				95.45	
44-F1	170.9	149.6	82.04	1.24	84.81	2.39	90.63	1.41	89.25	2.03
38	170.0	128.2	93.01	1.86	93.25	2.90	93.33	1.67	100.89	2.60
39	171.0	128.9	85.41	1.86	98.19	3.07	90.40	1.69	90.51	2.45
34-H2	154.5	121.8	90.02	2.09	94.84	3.09	90.12	1.81	98.37	2.66
33-G2	165.7	121.1	92.98	1.98	94.55	3.00	97.75	1.50	96.39	2.60
35	188.1	123.3	90.59	1.26	90.40	2.30	91.38	1.19	94.19	2.00
13	158.8	64.0	87.86	1.56	83.51	3.00	91.49	1.45	91.96	2.70
10	153.5	57.6	88.74	2.09	90.13	3.70	93.03	1.78	93.01	3.40
31	160.0	120.1	87.00	2.36	86.34	3.35	-	-	86.59	2.85
29-F2	170.9	118.4	-	-	96.84	2.93	93.87	1.66	95.87	2.46
21	189.7	87.2	95.54	0.99	95.77	2.20	96.43	1.04	89.07	1.79
19	174.5	74.5	95.99	1.13	90.58	2.36	88.84	1.08	86.67	1.94
2-A2	161.2	45.2	92.44	2.01	92.47	4.09	-	-	-	-
7	162.7	55.6	92.13	1.81	87.97	3.49	-	-	-	-
4-B2	154.7	49.7	97.60	1.98	98.14	3.89	-	-	-	-
12	170.4	63.3	92.83	1.86	100.80	3.75	-	-	-	-
22	178.1	88.4	94.25	1.31	94.54	2.55	-	-	91.74	2.16
11	163.6	57.9	92.48	1.58	94.47	3.22	-	-	92.66	2.78
20	185.2	85.0	93.88	1.10	96.81	2.36	-	-	94.69	1.99
16	184.2	72.9	98.24	1.12	99.06	2.40	-	-	95.48	2.03
6	178.3	53.7	90.83	1.34	97.52	3.07	-	-	92.83	2.57
N			20		21		11		17	
Mean			91.69		93.38		92.47		92.95	
S.D.M.			4.04		4.81		2.74		3.88	
S.E.M.			0.91		1.05		0.83		0.94	
17-C3	163.6	73.7	108.33	1.66	91.62	3.17	-	-	96.89	2.62
18-C2	163.6	73.7	101.90	1.67	98.43	3.33	92.94	1.77	87.40	2.48
23-C1	163.6	88.9	98.55	1.56	89.03	2.80	89.86	1.55	83.98	2.15
25-D3	161.2	97.5	90.39	2.57	94.50	3.98	94.58	2.36	92.37	3.21
26-D2	161.2	102.3	103.38	2.74	90.61	3.64	87.43	2.07	95.94	3.04
28-E2	166.4	113.8	105.91	1.60	94.77	2.84	92.90	1.59	95.70	2.32
36-J2	178.5	125.3	90.70	1.53	84.26	2.35	89.10	1.49	-	-
37-D1	161.2	128.0	97.16	2.07	95.11	3.16	94.53	1.78	95.31	2.54
40-E1	166.4	130.9	99.82	1.47	92.61	2.50	89.80	1.39	86.70	2.00
43-J1	178.5	147.8	91.82	1.39	87.90	2.26	87.84	1.28	88.84	1.86
46	182.9	157.0	97.36	1.33	79.23	2.16	89.35	2.04	95.23	1.99
N			11		11		10		10	
Mean			98.67		90.73		90.83		91.84	
S.D.M.			6.02		5.46		2.67		4.69	
S.E.M.			1.82		1.64		0.84		1.48	

*Coefficient of variation.

The S.D. in counts per minute associated with each $^{39,40}K$ measurement was calculated as follows:

$$S.D. = \sqrt{\frac{B}{T_1} + \frac{C}{T_2}}, \qquad (3)$$

where

$\underline{B}$ = background count rate in counts per minute,

$\underline{T}_1$ = length of time in minutes background was counted,

$\underline{C}$ = gross counts per minute from subject,

$\underline{T}_2$ = length of time in minutes subject was counted.

A modified coefficient of variation (C.V.) of each K determination, defined as percentage of the net count rate, % = (S.D./C - B) x 100, is given with each ratio in Table 25. This percentage reflects only the statistical uncertainty introduced into the ratio by the $^{39,40}K$ measurement and does not include the statistical uncertainty present in the ^{42}K measurements. The statistical uncertainty (which is less than 1%) present in the ^{42}K count rates (in $\underline{G}$ factors) has been ignored in order to emphasize the magnitude of the variability present in K measurements with all of these techniques. The S.D. associated with the isotopic dilution measurement amounted to 3.2% and was ignored since it is common to all ratios given for a particular subject.

In order to simplify Table 25, only the exchangeable K ratios based on the K contents calculated from the photopeak energy bands are given. The subjects are listed in the table in the sequence that they were measured and not by weight. Data on subjects who were measured more than once are designated by a letter and chronological number.

The ratios for the first 15 subjects listed in the table are included only to permit a comparison of the ratios found for each individual subject by the three whole-body counter techniques. The absolute magnitude of these 15 ratios is known to be questionable and should not be considered to represent the exchangeable K ratio for these subjects. The counting system purchased expressly to measure the ^{42}K content of the urine yielded slightly erratic background count rates during the period that the first 15 subjects were measured. Although no individual measurement was grossly incorrect, a statistical analysis of a series of repetitive determinations demonstrated that a larger variation existed than had been predicted. This counter was repaired by the manufacturer, and stable reproducible measurements were obtained thereafter. The errors introduced into the urine measurements did not significantly influence the excretion correction applied to the $\underline{G}$ factors but did significantly influence the exchangeable ratios.

These ratios obtained for the remaining 32 subjects prove conclusively that any individual K measurement made by any technique can contain a sizeable error. In some subjects, three techniques yield the same values, whereas the fourth yields a much different value. Ratios of 93.01, 93.25, and 93.33, respectively, were found for subject 38 with the 4-pi liquid counter, the 8 x 4 TC, and 7-crystal technique, but a ratio of 100.89 was found with the log TC. Reanalysis of the original data obtained with the log crystal revealed that the calculations are correct. For subject 44-F1, the 4-pi liquid counter, 8 x 4 TC, 7-crystal, and log TC techniques yielded ratios of 82.04, 84.81, 90.65, and 89.25, respectively. The agreement between the last two techniques plus the preconceived belief that the exchangeable K ratio should be about 90% would lend support to the assumption that the 4-pi liquid counter and the 8 x 4 TC measurements are low; however, this is an assumption, not a proven fact.

The series of 44 measurements was divided into three groups, and the mean, S.D. of mean, and S.E. of mean for the measurements made by each technique are given in Table 25. The first group of 15 subjects includes measurements made while the urine ^{42}K counter was erratic; the second group of 21 subjects includes healthy individuals who followed a normal life at home; and the third group consists of 11 measurements made of 5 persons who were fasting in a hospital metabolic ward but who followed a prescribed course of exercise and were not at bed rest.

The mean ratios for the first group for the 4-pi liquid counter and log TC agree fairly well, while the mean ratio for the 8 x 4 TC is appreciably higher ($\simeq$2%). The mean ratios for all techniques for the second group of 21 subjects agree surprisingly well. The grand mean of the four individual means is 92.62 or within 1 S.E. of mean for each of the techniques except the 4-pi liquid counter, where the mean is only 0.02 beyond a single S.E. of mean of 0.91.

The means of the ratios for the third group of 5 subjects in Table 25 with the 8 x 4 TC, the 7-crystal, and the log TC agree but are somewhat lower than those for the second group with the same techniques. The mean value for the 4-pi liquid counter is extremely high and does not agree with those for the other techniques for this group nor with the ratio found with the 4-pi liquid counter for the second group. Undoubtedly, the measurements of the 4 subjects for whom ratios of over 100% were found are erroneous; however, no reason can be advanced for these discrepancies.

The slightly lower ratios for the 11 measurements of the third group with the 8 x 4 TC technique probably reflect one change in subject position procedure. Except for this series of measurements, each subject was told to sit with his knees resting out against the arm rests of the chair and with his hands clasped in his lap. Measurements of ^{42}K made several years ago showed that the count rate would decrease several percent if a subject

placed his arms alongside his body in the chair and that the count rate might increase a few percent if he held his knees together, in which position the knees are slightly closer to the crystal. For the last series of measurements, the subject's knees were taped in the desired position (with easily broken masking tape to avoid subject fatigue) and he wore gloves with fingers that had been sewn together. Consequently, the subject remained in the same position even though he may have slept during the measurement. This procedure may account for the absence of any ratios as high as 100 such as were seen in the second group.

Variability of Exchangeable K Ratios

A controversy exists about the relationship between the K value measured by the isotopic dilution technique and the actual K content of the body. Some investigators maintain that all the body K is readily exchangeable and that the value found by the dilution technique is the true value. However, we found that the mean exchangeable ratios given by each technique were about 0.92.

An analysis of the exchangeable K ratios (Table 25), which ranged from 86 to 95% for the individual subjects, seems to suggest that this ratio is consistent among all subjects. The values for the standard deviation of the mean of the exchangeable ratios determined by the 7-crystal technique for the two groups of subjects (2.74 and 2.67%) is less than the 3.2% standard deviation present in the isotopic dilution measurement alone. The uncertainty in the normal K measurement has been ignored. When the two groups of subjects are pooled, the 21 exchangeable K ratios yield a mean ratio of 91.65%. Only 4, instead of the acceptable 7, ratios fall over 1 standard deviation from this mean, and no ratios (1 acceptable) fall outside 2 standard deviations. For 3 subjects (35, 21, and 43-J1) of these 4 whose ratios fell more than 1 standard deviation beyond the mean, practically the same exchangeable K ratios were found with two of the other whole-body counter techniques. Consequently, the variability in the exchangeable ratios found with the 7-crystal sum represents either statistical counting uncertainties in the isotopic dilution measurements or differences in the ratios among subjects. However, the 3.2% statistical uncertainty associated with the isotopic dilution measurement overshadows any differences that may exist among the individual subjects.

The large variability among the exchangeable K ratios found with the 4-pi liquid counter, 8 x 4 TC, and log TC measurement techniques must be attributed to errors in counting either the normal body K or the ^{42}K in the body.

Exchangeable K Ratios Based on Regression Line G Values

The data were recalculated to determine if an average calibration factor based on the subject's weight could be employed for K measurement or whether it was really necessary to administer ^{42}K to every subject for accurate results. The K content of each subject was recalculated with the G factor given by the regression line for a person of his weight. The exchangeable K ratios obtained for the 4-pi liquid counter, 8 x 4 TC, and log TC based on those K values are given in Table 26. The 7-crystal sum results were not recalculated because of the limited number of measurements included in each series.

TABLE 26

Exchangeable K ratio calculated with regression line G factor

Subject	Height, cm	Weight, kg	4-pi liquid		8 x 4 tilting chair		7-crystal sum		Log tilting chair	
			Ratio	C.V.	Ratio	C.V.	Ratio	C.V.	Ratio	C.V.
41	172.8	136.6	81.31	1.28	89.10	2.37	-	-	88.07	1.98
47	186.9	167.1	70.02	1.08	84.87	2.13	-	-	75.64	1.65
42	160.5	143.1	105.79	2.16	104.98	3.05	-	-	111.71	2.69
1-A1	161.2	43.9	91.02	2.00	97.60	3.92	-	-	96.19	3.16
3-B1	154.7	48.5	107.51	2.00	112.25	3.86	-	-	106.89	2.98
5	161.4	52.7	98.59	2.00	95.95	3.61	-	-	95.12	2.88
8	163.0	55.9	108.01	1.84	113.72	3.58	-	-	111.86	2.84
32-H2	154.5	121.0	119.13	1.95	91.74	3.14	-	-	89.87	2.74
27	165.1	102.5	97.03	1.38	101.84	2.64	-	-	-	-
30-G1	165.7	119.7	99.27	1.96	96.76	3.02	-	-	-	-
45	159.2	150.4	-	-	102.17	2.97	-	-	107.25	2.58
24	184.1	92.9	86.16	0.99	87.44	2.10	-	-	86.34	1.70
15	179.9	71.8	88.75	0.98	92.60	2.22	-	-	93.39	1.81
9	167.7	56.4	71.69	1.68	80.87	3.62	-	-	84.59	3.02
14	168.9	70.3	84.76	1.25	89.53	2.68	-	-	85.82	2.12
Mean			93.52		96.10				94.83	
44-F1	170.9	149.6	81.85	1.24	94.15	2.39	90.63	1.41	94.90	2.03
38	170.0	128.2	100.45	1.86	97.72	2.90	93.33	1.67	105.33	2.60
39	171.0	128.9	95.45	1.86	99.59	3.07	90.40	1.69	92.53	2.45
34-H2	154.5	121.8	91.09	2.09	108.47	3.09	90.12	1.81	109.41	2.66
33-G2	165.7	121.1	97.52	1.98	87.89	3.00	97.75	1.50	92.70	2.60
35	188.1	123.3	84.49	1.26	79.63	2.50	91.38	1.19	81.72	2.00
13	158.8	64.0	92.42	1.56	87.35	3.00	91.49	1.45	92.92	2.70
10	153.5	57.6	95.52	2.09	87.72	3.70	93.03	1.78	93.69	3.40
31	160.0	120.1	88.23	2.36	78.54	3.35	-	-	78.05	2.85
29-F2	170.9	118.4	-	-	100.01	2.93	93.87	1.66	98.08	2.46
21	189.7	87.2	93.91	0.99	95.16	2.20	96.43	1.04	87.59	1.79
19	174.5	74.5	95.37	1.13	88.52	2.36	88.84	1.08	83.49	1.94
2-A2	161.2	45.2	91.23	2.01	95.13	4.09	-	-	-	-
7	162.7	55.6	99.43	1.81	96.74	3.49	-	-	-	-
4-B2	154.7	49.7	100.05	1.98	100.02	3.89	-	-	-	-
12	170.4	63.3	95.92	1.86	102.41	3.75	-	-	-	-
22	178.1	88.4	97.69	1.31	95.86	2.55	-	-	94.31	2.16
11	163.6	57.9	94.21	1.58	96.24	3.22	-	-	95.76	2.78
20	185.2	85.0	94.13	1.10	97.15	2.36	-	-	95.55	1.99
16	184.2	72.9	97.25	1.12	97.61	2.40	-	-	96.49	2.03
6	178.3	53.7	90.11	1.34	98.83	3.07	-	-	94.40	2.57
N			20		21				17	
Mean			93.82		94.51				93.34	
S.D.M.			4.91		7.26				7.71	
S.E.M.			1.10		1.58				1.87	
17-C3	163.6	73.7	95.88	1.66	93.13	3.17	-	-	95.94	2.62
18-C2	163.6	73.7	96.35	1.67	101.94	3.33	92.94	1.77	91.37	2.48
23-C1	163.6	88.9	97.68	1.56	91.08	2.80	89.86	1.55	84.57	2.15
25-D3	161.2	97.5	91.78	2.57	93.67	3.98	94.58	2.36	89.88	3.21
26-D2	161.2	102.3	105.14	2.74	90.12	3.64	87.43	2.07	93.00	3.04
28-E2	166.4	113.8	96.96	1.60	95.99	2.84	92.90	1.59	98.97	2.32
36-J2	178.5	125.3	93.15	1.53	78.04	2.35	89.10	1.49	-	-
37-D1	161.2	128.0	96.17	2.07	95.48	3.16	94.53	1.78	92.04	2.54
40-E1	166.4	130.9	99.00	1.47	94.65	2.50	89.80	1.39	91.37	2.00
43-J1	178.5	147.8	90.16	1.39	87.59	2.26	87.84	1.28	87.90	1.86
46	182.9	157.0	92.38	1.33	85.13	2.16	89.35	2.04	98.04	1.99
N			11		11				10	
Mean			95.88		91.53				92.31	
S.D.M.			4.12		6.34				4.44	
S.E.M.			1.24		1.91				1.98	

The mean ratios obtained for the second group of about 20 subjects were 2.13, 1.13, and 0.39% higher for the 4-pi liquid counter, 8 x 4 TC, and log TC, respectively, when the regression line $\underline{G}$ values were used than when the subject's own $\underline{G}$ factor was used. The standard deviation of the mean was slightly larger for the 4-pi liquid counter but considerably larger for the two tilting-chair techniques. The acceptable exchangeable K ratios of 93.01 and 90.58 for subjects 38 and 35, respectively, obtained with the 4-pi liquid counter became 100.45 and 84.49, respectively (Table 26). In the case of the 8 x 4 TC and log TC measurements, the exchangeable K ratios of 90.4 and 94.19 found by the two techniques for subject 35 decreased to 79.63 and 81.72 and the already high exchangeable ratios of 94.84 and 98.37 for subject 34-H2 increased to the impossibly high values of 108.47 and 109.41.

The observations that the exchangeable K ratios for these subjects agree with the mean exchangeable K ratio for the group when their own $\underline{G}$ factors were used but differ greatly from the mean when the regression line value of $\underline{G}$ was used suggests (1) that the % $\underline{G}$ spread observed for these subjects does, in fact, reflect different counting efficiencies for K in the body, and (2) that a very significant error will be introduced for some subjects in 4-pi liquid, 8 x 4 TC, and log TC measurements if an average calibration factor is used.

When the regression line $\underline{G}$ factors were used for the third group of 11 subjects the results for the 8 x 4 TC and log TC ratios were approximately the same as for the second group. The mean ratios for these two techniques increased 0.80 and 0.47%, respectively, and a greater spread in exchangeable K ratios was noted. However, results were considerably different for the 4-pi liquid data. The mean ratio for the 4-pi liquid counter decreased 2.79%, and the S.D. of mean decreased significantly from 6.02 to 4.12%. The impossibly high ratios of 108.33 and 101.90 (Table 25) found for subjects 17-C3 and 17-C2 (same subject at different times) decreased to 96.85 and 96.46, respectively, and the ratios of 105.91 for subject 28-E2 decreased to 97.46. The ratios of 103.38 for subject 26-D2 increased slightly. The exchangeable ratios for these subjects based on the 4-pi liquid counter, which decreased to a physically acceptable value, suggest that the ^{42}K measurements made during this third series must be slightly erratic. Significantly, the mean ratio also decreased to a value nearer the mean ratios found by the other techniques.

In order to obtain comparable data for the 7-crystal sum, the exchangeable K ratios of the last 10 measurements in Table 25 were recalculated with the $\underline{G}$ factors predicted by the regression lines found to fit this limited series of 10 subjects. It should be emphasized that for the 4-pi liquid counter, 8 x 4 TC, and log TC techniques, the regression line found to fit these 10 subjects, rather than the line found to fit the entire

series, was used. The exchangeable K ratios for each subject for each method as well as the mean, S.D. of mean, and S.E. of mean of the ratios for each technique are given in Table 27.

TABLE 27

Exchangeable K ratios calculated for 10 subjects with regression G values

Subject	Height, cm	Weight, kg	4-pi liquid		8 x 4 tilting chair		7-crystal sum		Log tilting chair	
			Ratio	C.V.	Ratio	C.V.	Ratio	C.V.	Ratio	C.V.
17-C3	163.6	73.7	100.40	1.66	92.47	3.17	-	-	95.74	2.62
18-C2	163.6	73.7	100.89	1.67	101.21	3.33	94.96	1.77	91.19	2.48
23-C1	163.6	88.9	101.56	1.56	90.39	2.80	89.40	1.55	84.29	2.15
25-D3	161.2	97.5	95.04	2.57	92.94	3.98	93.54	2.36	89.51	3.21
26-D2	161.2	102.3	108.62	2.74	89.41	3.64	88.71	2.07	92.58	3.04
28-E2	166.4	113.8	99.63	1.60	95.20	2.84	95.73	1.59	98.42	2.32
36-J2	178.5	125.3	95.21	1.53	77.37	2.35	85.63	1.49	-	-
37-D1	161.2	128.0	98.17	2.07	94.66	3.16	95.73	1.78	91.42	2.54
40-E1	166.4	130.9	100.86	1.47	93.83	2.50	91.40	1.39	90.73	2.00
43-J1	178.5	147.8	91.18	1.39	86.79	2.26	85.53	1.28	87.15	1.86
46	183.0	157.0	93.03	1.33	84.34	2.16	90.85	2.04	97.14	1.99
Mean			98.60		90.74		91.12		91.77	
S.D.M.			4.84		6.34		3.84		4.40	
S.E.M.			1.46		1.91		1.22		1.39	

The mean ratio for the 7-crystal sum increased slightly from 90.83 (Table 25) to 91.12 (Table 27), and the S.D. of mean increased from 2.67 to 3.84. A slightly greater range in exchangeable ratios exists for the individual subjects--85.53 to 95.73 (Table 27) versus 87.43 to 94.58 (Table 25)--when the regression line G values are used.

For the 4-pi liquid counter, the exchangeable K ratios for one subject increased to the impossibly high value of 109%. However, the exchangeable K ratios for subjects 17-C3 and 28-E2 decreased from the impossibly high values of 108.33 and 105.91 to physically possible values of 100.55 and 100.13, respectively. The S.D. of mean also decreased from 6.02 when the person's own G factor was used to 4.85 when the regression line G factor was used. These results suggest also that the ^{42}K measurements were in error.

These extremely divergent exchangeable K ratios obtained by the 4-pi liquid counter, 8 x 4 TC, and log TC techniques when the regression line G factors are used demonstrate that any isolated single measurement of a subject may contain as much as a 10% error if the person is not given ^{42}K to calibrate the counter for his own unique body build.

Comparison of G Factors Found at Different Positions along the Body

Analyses were performed to determine if the variability observed with the tilting-chair technique or the 4-pi liquid counter could be explained with results obtained at the seven positions along the body. The results of one analysis are presented since these are pertinent to other techniques currently being tested by other investigators.

The net ^{42}K count rate obtained when the 8 by 4 crystal was located over the subject at each of 7 positions was divided into the count rate obtained from the same amount of ^{42}K in a bottle on the tray at 40 cm. A G factor was thus obtained for each of the 7 positions for each of 9 subjects measured with the 8 by 4 crystal 30 cm above the bed.

The G factors for each of the 7 positions for 9 subjects were fitted with regression lines. The % G spread that the observed G factors fell above or below the regression line for each position is given in Table 28. In addition, the G factors obtained with the 7-crystal sum, the 4-pi liquid counter, 8 x 4 TC, and log TC for these same 9 subjects were also fitted with regression lines, and the % G spread is given in the table. The sign associated with the % G spread is opposite to the variation in ^{42}K count rate from the human. That is, if the ^{42}K yielded a higher count rate than predicted, the observed G factor, $^{42}K_{bottle}/^{42}K_{man}$, would be less than the regression line and thus carry a negative sign.

TABLE 28

% G spread observed for seven crystal positions and for each technique

Subject	Height, cm	Weight, kg	Crystal position 1	2	3	4	5	6	7	7-crystal sum	4-pi	8 x 4 TC	Log TC
						Compton energy band							
2-A2	161.2	45.2	-9.86	-3.42	-1.23	-0.20	1.05	4.74	-1.91	-1.52	-4.43	-1.54	-0.18
4-B2	154.7	49.7	4.19	-1.04	-2.49	-1.32	-0.08	-0.94	-1.84	-0.83	-0.47	5.32	-2.90
10	153.5	57.6	9.43	4.66	-2.34	-2.56	-1.28	6.17	7.05	1.27	5.01	-5.91	-0.38
12	170.4	63.3	-7.36	-3.92	0.62	0.94	1.64	-2.97	-1.20	-1.18	1.14	-1.39	-1.12
13	158.8	64.0	11.06	2.50	0.98	1.84	1.78	0.45	3.57	2.66	3.01	2.23	1.92
19	174.5	74.5	0.80	2.69	5.63	0.38	-5.14	-7.91	-3.23	0.20	-2.09	-0.30	1.46
21	189.7	87.2	-7.14	0.77	2.58	3.22	1.70	-4.16	-3.93	0.32	-2.41	2.93	3.78
33-G2	165.7	121.1	-8.00	-6.48	-7.44	-5.79	1.39	13.17	4.17	-3.59	6.26	1.87	2.48
35	188.1	123.3	9.82	4.88	4.32	3.86	-0.85	-6.70	-2.10	2.83	-5.38	-2.73	-4.77
						Photopeak energy band							
2-A2	161.2	45.2	-12.60	-3.84	-3.21	-0.76	2.11	5.62	-0.53	-2.21	-4.43	-0.58	-0.11
4-B2	154.7	49.7	6.50	-1.06	-1.44	1.26	0.34	0.71	-0.24	0.38	-0.47	-0.78	-2.06
10	153.5	57.6	6.60	2.71	-0.71	-3.48	-0.92	5.54	7.90	0.89	5.01	-4.01	0.45
12	170.4	63.3	-7.57	-1.94	0.23	0.69	2.81	-0.24	0.19	-0.40	1.14	1.13	0.48
13	158.8	64.0	14.29	2.82	1.30	1.69	-2.00	-2.07	-3.42	1.83	3.01	4.23	1.66
19	174.5	74.5	2.68	1.30	6.11	0.22	-5.71	-10.19	-3.98	-0.12	-2.09	-0.93	-1.67
21	189.7	87.2	-7.09	3.25	1.04	1.63	2.94	5.64	-1.68	0.40	-2.41	2.84	2.15
33-G2	165.7	121.1	-6.23	-7.31	-4.14	-4.23	3.64	19.17	6.47	-1.57	6.26	1.69	4.68
35	188.1	123.3	6.66	4.70	1.16	3.23	-2.81	9.71	-3.97	0.87	-5.38	-3.29	-5.27

Very large % G spreads are observed for each crystal position. Of particular significance is the fact that while one person exhibits a negative value for position 1 over the head and a positive value for position 7 over the feet, a second subject exhibits the opposite result, and other subjects yield either positive or negative values at these 2 positions. Nevertheless, the G factors based on the sum of the count rates from the 7 positions exhibit a much smaller G factor spread than the 4-pi liquid counter, the 8 x 4 TC, or the log TC techniques. No explanation can be given for the large % G spread observed with the 4-pi liquid counter in view of the small spread found for the 7-crystal sum. The 2 techniques are similar and equivalent results would be expected.

The same analyses were performed with the data obtained by all 4 techniques for the 11 subjects included in the third group. In this case the 7-crystal measurements were made with the 8 by 4 crystal 35.8 cm above the surface of the bed. The subjects' weights ranged from 73.7 to 157 kg versus 45.2 to 123.3 kg for the first group. The G factors for each of the 7 positions exhibited approximately the same spread around the regression line as those for the previous group of subjects. Again, the G factors based on the sum count rate of 7 crystal positions fell very close to their regression line.

These large variations in % G spread values given in Table 28 demonstrate the impracticability of counting a supine subject with one or two stationary crystals. This analysis was included because some whole-body counter groups have proposed the use of an uncollimated scan technique whereby the crystal traverses a distance 60 to 80 cm along the body. If the resultant G factors were fitted with a regression line, they would fall above or below the line an amount approximately equal to the average of the three % G spread values (Table 28) that cover that length. A typical 75-cm scan along the torso would be equilvalent to positions 2, 3, and 4. The % G spread for subject 33-G2 for such a scan would be about -5%, while the spread for subject 35 would be about +2%. Consequently, these data suggest that the % G spread will be reduced as more crystals are employed.

G Factor for Same Subject at Different Total-Body Weights

A special study was conducted with a number of obese subjects to determine if the G factors obtained for a subject as he lost weight decreased along the regression line that was derived from many subjects of different weights. After the first series of K measurements was completed, the subject fasted for several weeks in a hospital metabolic ward. During the starvation period, the subject followed a prescribed course of exercise and remained active. The complete series of measurements was repeated approximately 1 week after the subject had terminated his fast. Measurements of the same subject are designated by letter and number in the tables; the number designates the sequence of the measurement. Measurements designated C, D, E, and J were made of subjects who successfully completed this program and lost 15.2, 30.5, 17.1, and 22.5 kg weight, respectively. Measurements 37, 26, and 25 in Table 20, designated D1, D2, and D3, were made of one subject before starvation, during a period when this subject resumed eating, and then at the end of a second starvation period.

With the 4-pi liquid counter, the G factors for subjects C1, D1, E1, and J1 before starvation fell 0.87, 1.01, 0.81, and 1.80% below the regression line (Table 22). After starvation the G factors for two of these subjects, C3 and E2, fell 11.48 and 8.44% below the G factors predicted by the regression line for subjects at their new weights. The new

G factors for subjects D3 and J2 were 1.54 and 2.71% above the regression line. Thus, the ^{42}K in subjects C3 and E2 was counted more efficiently after diet than would have been predicted from measurement of other subjects of the same weight.

With both tilting-chair techniques, the G factors based on the photopeak band for subjects C, D, and E changed about as predicted by the regression lines. For example, the G factor for the 8 x 4 TC for C1 before starvation was 2.31% above the line and for C3 after starvation it was 1.66% above the line. However, the G factor obtained for J2 after starvation decreased much faster than predicted, from 0.34% below the regression line to 7.38% below the line. Unfortunately, the log TC measurement was not obtained because of a technical error so it is not possible to compare 8 x 4 TC and log TC results for this subject.

Only 11 measurements were made with the 7-crystal technique with the 8 by 4 crystal located 35.8 cm above the bed. Consequently, the results are biased because of the limited number of G factors employed and the fact that all measurements were of the same subjects. It is noteworthy that the G factors did decrease with weight, approximately as predicted by the regression line found to fit these 11 measurements. Both G factors obtained for a subject agreed within about 1% whether they fell above or below the regression line. For example, the G factors for one subject (J1 and J2) were 2.63 and 3.89% below the regression line. Significantly, this was the one subject whose 8 x 4 TC G factor decreased much more than expected.

This analysis indicates that the G factors changed as the subjects lost weight but not, at least for the 4-pi liquid counter and 8 x 4 TC, as predicted by the regression line. The G factors obtained for any subject at two different total-body weights with the 7-crystal sum seemed to change as predicted by the slope of the regression line but not enough subjects were studied to prove it.

Weight/Height as the Independent Variable

Various investigators have suggested that the calibration factors would be more closely correlated to the weight/height ratios than to just the total weights.[4] Each time a regression analysis that employed weight was performed, a second regression analysis that employed weight/height was also performed. The results of these second analyses have been omitted since, for every whole-body counter technique, the mean G spreads obtained from these analyses based on weight/height were equal to or larger than those based on weight alone.

When the results of the analyses for individual subjects were compared, it was found that the G factors for some subjects fell closer to the

regression line based on weight/height than to the regression line based on total weight. However, the opposite effect occurred just as often, and as a result an equal or larger mean G spread occurred.

The use of weight/height might reduce the spread in G factors around the regression line if the subject's weight were more or less uniformly distributed along his body. Actually, the spread in G factors results because the weight is not uniformly distributed. Since the absorption of gamma rays is an exponential function of mass, the use of a linear average of the subject's weight does not correct for the nonlinear absorption.

Discussion of Previously Published Divergent Results

Some of the conclusions reached in this paper are contradictory to results published previously.[5] In the previous study we published the following observations: (1) the G factors found with the 8 x 4 TC for 24 patients who weighed between 50.3 and 95.3 kg fell within 3% of the mean G factor and did not depend upon the weight of the patients; (2) the G factors for 4 very obese patients who weighed between 142.1 and 164.8 kg were much larger than those for the lighter patients; (3) the G factors based on the count rate of any combination of, or of all the same, crystal positions had a much larger spread than those obtained with the 8 x 4 TC technique; and (4) the exchangeable K ratios found for the 29 patients were dependent upon the weight of the patients. The exchangeable K ratio varied from about 89% for the lighter patients to slightly over 100% for the very obese patients.

In the previous analyses, the G factors for the series of 24 patients had been correlated with weight, weight/height, and exponential relationships of weight/height. Recently, the entire series of 28 G factors was fitted with the regression line, $\log_{10} G = a + b(w_{kg})$. As found for the series of 44 subjects discussed above, the G factors based on the Compton energy band do not support a regression line that has a significant slope. However, approximately the same parameters were found for the regression line based on the photopeak G factors for this earlier series of 28 patients as for the current series of 44 subjects. The G factors for some of the larger patients fell 10% above or below the regression line, and the G factor obtained for the smallest patients (50.3 kg) fell 10% above the regression line. Notably, none of the G factors obtained for the smaller subjects included in the present study deviated more than 5% from the regression line.

One explanation can be advanced for the high G values found for the small patients, the divergent G factors found with the 7-crystal technique, and the dependence of exchangeable K ratios on weight. The 29 persons included in the previous study were all patients who were at bed rest in a hospital. Consequently, the divergent G factor probably reflects a non-normal distribution of ^{42}K in their bodies.

The seemingly divergent results obtained for the patients in the earlier study cannot be attributed to any errors in measurement for several reasons: (1) practically the same equipment and counting techniques were used for both studies, (2) approximately the same parameters were found for the regression line, and (3) the same count rate per gram of $^{39,40}K$ was found during both studies. Consequently, the exchangeable K ratios are probably correct.

Conclusions

The results of these analyses have demonstrated that: (1) the calibration factors for all whole-body counter techniques are dependent upon the weight of the subject; (2) the single mathematical expression, $\log_{10} G = a + b(w_{kg})$ will fit the curve of calibration factors obtained for subjects whose weights range from 43.88 kg (96.7 lbs) to 157 kg (345 lbs); (3) the actual calibration factor found for a particular subject may differ by as much as 10% from the value predicted by the regression line; (4) the exchangeable K content of the body as measured by the isotopic dilution technique is very close to 92% of the total-body K for all active subjects, including those who have starved for several weeks and lost considerable weight; (5) the calibration factors and exchangeable K ratios obtained with the 7-crystal technique did not exhibit the variability observed with the other techniques; and (6) every subject should be given ^{42}K in order to obtain the correct calibration factor for his body build, if very accurate K measurements are desired.

References

1. C. E. Miller. An experimental evaluation of multiple-crystal arrays and single-crystal techniques. Whole-Body Counting. International Atomic Energy Agency, Vienna, 1962, pp. 81-120.

2. J. E. Christian, W. V. Kessler, and P. L. Ziemer. A 2-pi liquid scintillation counter for determining the radioactivity of large samples including man and animals. Intern. J. Appl. Radiation Isotopes 13, 557-564 (1962).

3. A. P. Remenchik and C. E. Miller. The measurement of total body potassium in man and its relation to gross body composition. Whole-Body Counting. International Atomic Energy Agency, Vienna, 1962, pp. 331-339.

4. L. D. Marinelli. Geometrical and physical parameters in whole-body gamma-ray spectrometry measurements. Argonne National Laboratory Radiological Physics Division Annual Report, July 1965 through June 1966. ANL-7220, pp. 31-41.

5. C. E. Miller and A. P. Remenchik. Problems involved in accurately measuring the K content of the human body. Ann. N.Y. Acad. Sci. 110, 175-188 (September 1963).

BODY COMPOSITION ESTIMATES DERIVED FROM POTASSIUM MEASUREMENTS*

Alexander P. Remenchik,** Charles E. Miller, and Wayne V. Kessler†

Several investigators have suggested that body potassium may be used as an estimator of body solids, cell mass, muscle mass, lean body mass, total-body fat, and in conjunction with body-water measurements as an estimator of muscle mass, adipose tissue and muscle-free lean tissue.[1-5] Each of these investigators has made crucial assumptions while formulating his model, and for man it has been impossible to evaluate directly the validity of the models that have been proposed. Our purpose is to review certain evidence bearing upon these assumptions, to examine the appropriateness of these models in view of this evidence, and to discuss the use of body potassium measurements in clinical medicine.

Potassium as an Estimator of Fat Content of Man

Since we cannot dissect and dissolve the humans we study and thus validate our indirect techniques, we must make inferences about the validity of specific techniques for man from validation studies of animals. One selects a method that has been shown to be valid for animals, assumes it is valid for man, formulates specific predictions for man predicated on this assumption and designs some experiments to test these predictions. For the evaluation of potassium as a predictor of body fat we elected to use body water as an estimator of fat-free tissue. Our review of the data suggested to us that body water is a reliable estimator of fat-free tissue. Keys and Brozek,[6] in their review entitled, "Body Fat in Adult Man," stated that their analysis of the data of Pace and Rathbun[7] indicated that the water content of lean tissue was dependent upon fatness. However, this conclusion was based upon erroneous calculations, which fact they have subsequently admitted in private correspondence with one of us.[8] As a matter of fact, it is not appropriate to calculate a simple summary statistic for the data of Pace and Rathbun, as is readily evident from an examination of a plot of their data (Figure 13). It is apparent one cannot define an elliptical field for these distributions. This is still the case if one separates the sexes, males (Figure 14) or females (Figure 15). Pitts,[9] after reviewing his own observations and data reported from other laboratories, concluded that the water

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content of lean tissue is not influenced by fat content of the carcass. We agree with his interpretation of the data. The variance of water content of fat-free tissue of different species is remarkably small as illustrated in Figure 16. One may infer from these data that the water content of fat-free tissue is a fundamental biological constant for any species. Crucial, of course, to this discussion are data with respect to the composition of fat-free adipose tissue of man. A limited number of analyses of adipose tissue[10] had indicated that the water content of fat-free adipose tissue is approximately 70% (Figure 17), while the potassium content is approximately 25 mEq/kg (Figure 18). Thus, fat-free adipose tissue has a water content approximately that of other tissue, but the potassium content is very much less than that of muscle and viscera.* We would predict from these data that the specific gravity of fat-free adipose tissue is less than the specific gravity of fat-free eviscerated carcass and, indeed, Pitts has reported this is the case.[9] Therefore, we predicted that potassium estimates of fat calculated by the method of Forbes[2] will overestimate the fat content of man, and this is indeed so,

$$F = {}^{40}K_B/68$$

as illustrated in Figure 19 for the 8 by 4 crystal technique, and in Figure 20 for the liquid scintillation counter technique. It is evident that for each subject fat content estimated from potassium lies above the line $y = x$. This overestimate is also the case for potassium determined by the other techniques. The diluting effect of fat-free adipose tissue can be illustrated in another way. If we compute the lean body mass content of potassium and plot this against % body fat, we observe a significant negative regression (Figure 21). The mean potassium content of fat-free lean tissue obtained by extrapolation of the regression lines calculated for each technique to 0% fat content is 2.55 g/kg (Table 29). This is less than the mean of 2.68 g/kg obtained from analysis of cadavers (Table 30). The discrepancy may be due to the fact that body water is overestimated by tritium dilution techniques. In a footnote in his article Pitts stated,[9]

> "On human data from various sources, a significant coefficient of correlation between fatness and FFBW has not been encountered. While this circumstance suggests that the factors producing such a correlation in guinea pigs and steers are nonoperative in man, many additional and uncontrolled variables in man may mask any correlation which might otherwise be present."

*After this essay was presented, Dr. Gilbert Forbes brought to our attention some data he had reported in a footnote in an article of his.[11] He stated, "Analysis of 12 samples of adipose tissue from exsanguinated rat, dog and rabbit revealed 41-93% fat (average 80%); on a fat-free basis water content was rather uniform (81%); sodium, chloride, and potassium concentrations were 122, 134 and 68 mEq/l of water, respectively." It is evident from these data that the potassium/water ratio of fat-free adipose tissue is <1 in contrast to a ratio >1 for muscle and viscera.

We have confirmed his expectations for man by plotting amount of fat versus lean body mass for men and for women (Figures 22 and 23). What can we say about fat estimates from potassium? Their utility depends upon the question. If we ask for an absolute estimate of fat then it is evident we are probably unable to provide this estimate by potassium measurements.

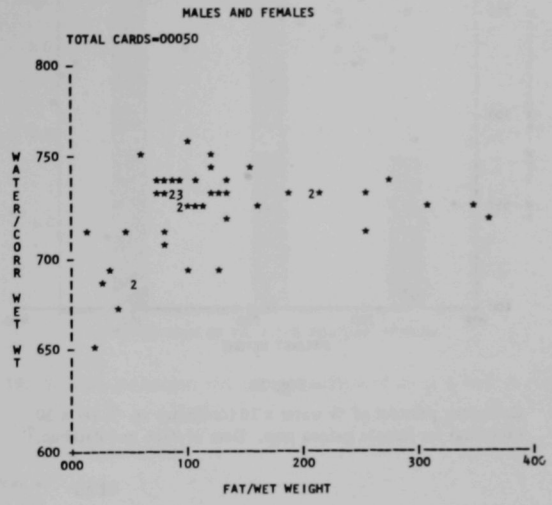

Fig. 13. Computer printout of % water x 10 (ordinate) vs. % fat x 10 (abscissa) for male and female guinea pigs. Data of Pace and Rathbun.[7]

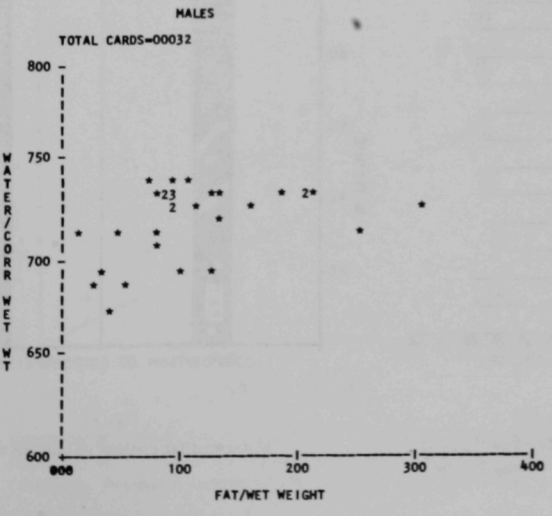

Fig. 14. Computer printout of % water x 10 (ordinate) vs. % fat x 10 (abscissa) for male guinea pigs. Data of Pace and Rathbun.[7]

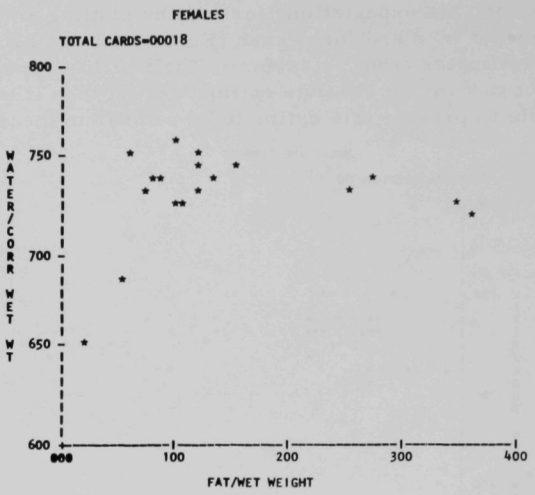

Fig. 15

Computer printout of % water x 10 (ordinate) vs. % fat x 10 (abscissa) for female guinea pigs. Data of Pace and Rathbun.[7]

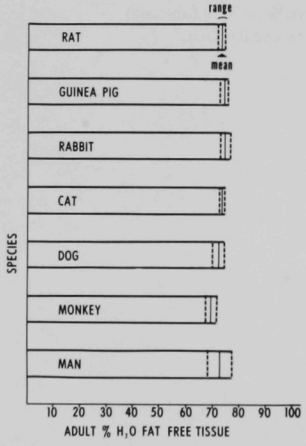

Fig. 16

Water content of fat-free tissue of different species. Compiled by Pace and Rathbun.[7]

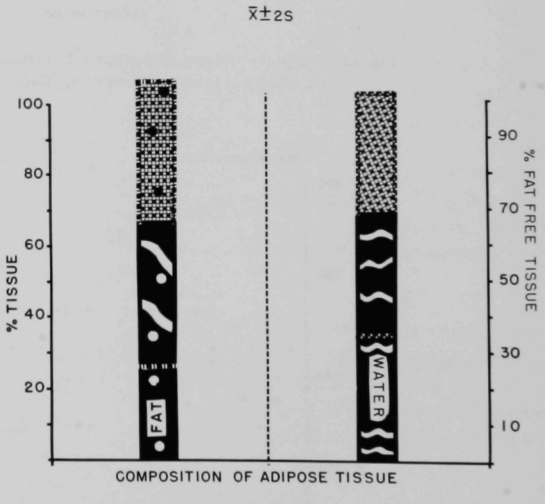

Fig. 17

Water and fat content of adipose tissue[10]

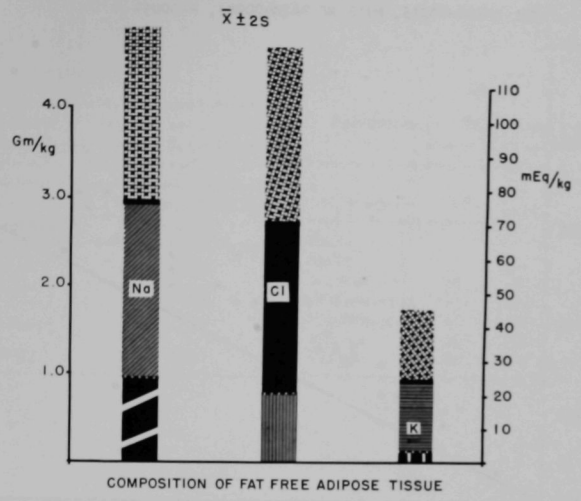

Fig. 18. Sodium, potassium, and chloride content of fat-free adipose tissue[10]

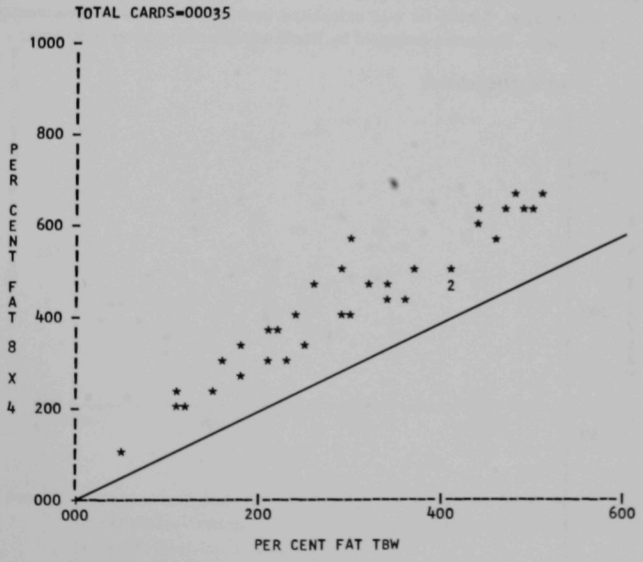

Fig. 19. Computer printout of % body fat x 10 calculated from potassium measurements (ordinate) vs. % body fat x 10 calculated from total-body water measurements (abscissa). Potassium measured by 8 x 4 crystal technique (ANL).

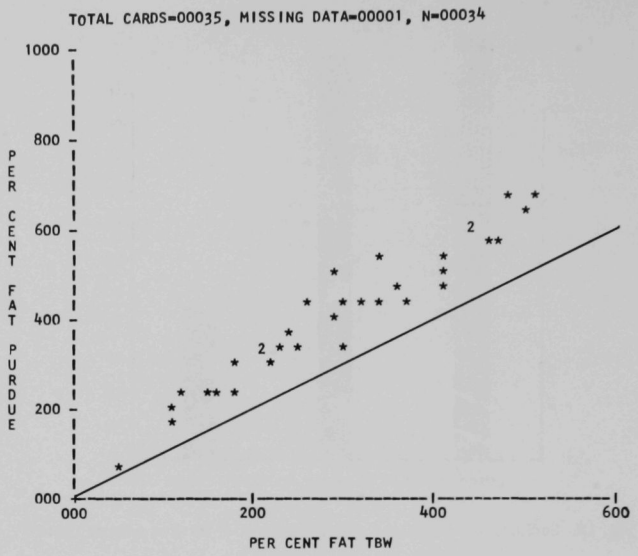

Fig. 20. Computer printout of % body fat x 10 calculated from potassium measurements (ordinate) vs. % body fat x 10 calculated from total-body water measurements (abscissa). Potassium measured by liquid scintillation counter technique.

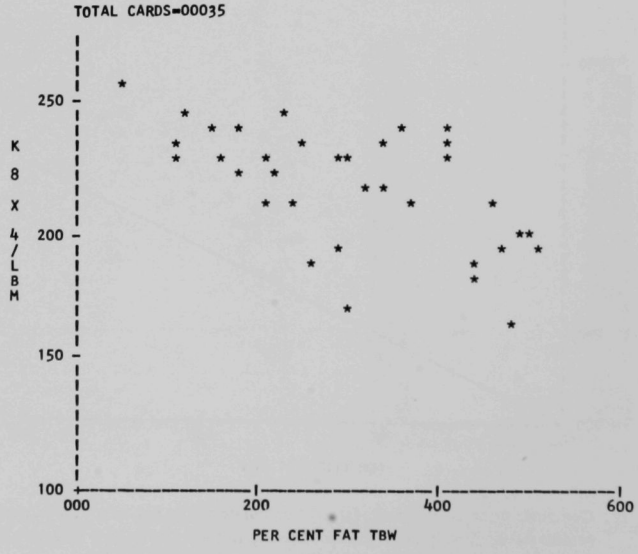

Fig. 21. Computer printout of (grams potassium per kilogram of lean body mass) x 100 (ordinate) vs. (% fat) x 10 from total-body water measurements (abscissa). Potassium measurements by 8 x 4 crystal technique.

TABLE 29

Potassium content of lean body mass calculated by computing intercept of regression line for plot of individual K_{B}/LBM versus % fat (from total-body water measurements)

Technique of measurement	K_{B}/LBM @ 0% fat, g/kg
$^{42}K_{B/0.91}$	2.49
$^{40}K_{B}$ (Purdue)	2.59
$^{40}K_{B}$ (8 x 4 crystal)	2.50
$^{40}K_{B}$ (log crystal)	2.61

TABLE 30

Potassium content of man obtained by direct analysis of cadavers[12]

Reference	Sex	Age	K, fat-free basis, g/kg
Shohl	-	-	2.61
Shohl	-	-	2.66
Widdowson	M	25	2.78
Widdowson	F	42	2.84
Widdowson	M	48	1.31
Forbes	M	46	2.60
Forbes	M	60	2.60

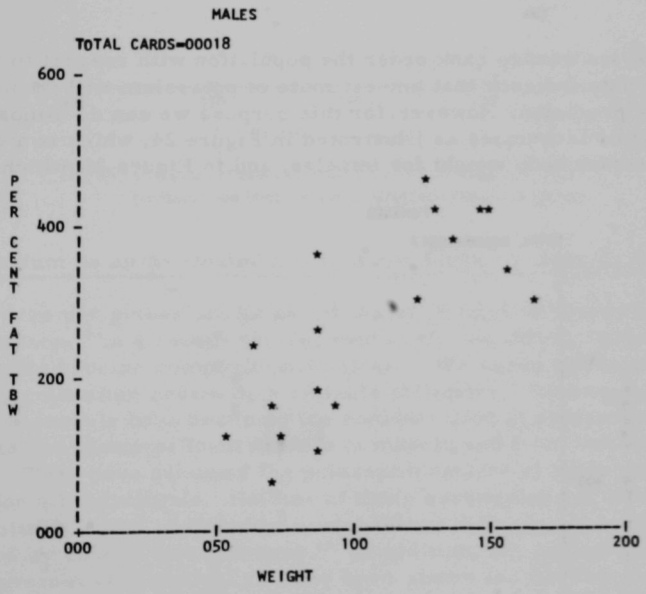

Fig. 22. Computer printout of % body fat x 10 calculated from total-body water measurements vs. lean body mass calculated from total-body water measurements (males)

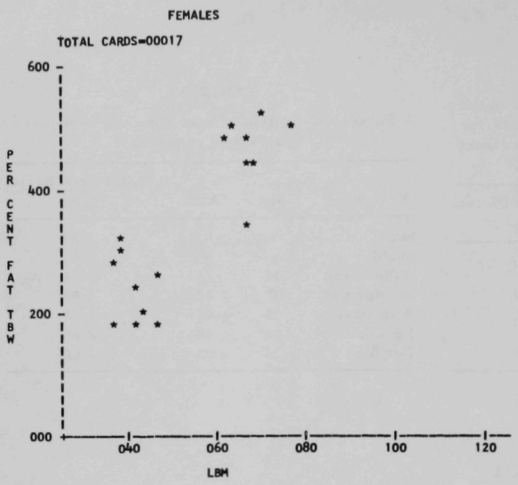

Fig. 23

Computer printout of % body fat x 10 calculated from total-body water measurements vs. lean body mass calculated from total-body water measurements (females)

Do we want to rank order the population with respect to fat content? Then the data indicate that any estimate of potassium will do so with a high degree of precision. However, for this purpose we can do almost as well by some simple techniques as illustrated in Figure 24, which is a plot of fat content versus body weight for females, and in Figure 25, which is for males.

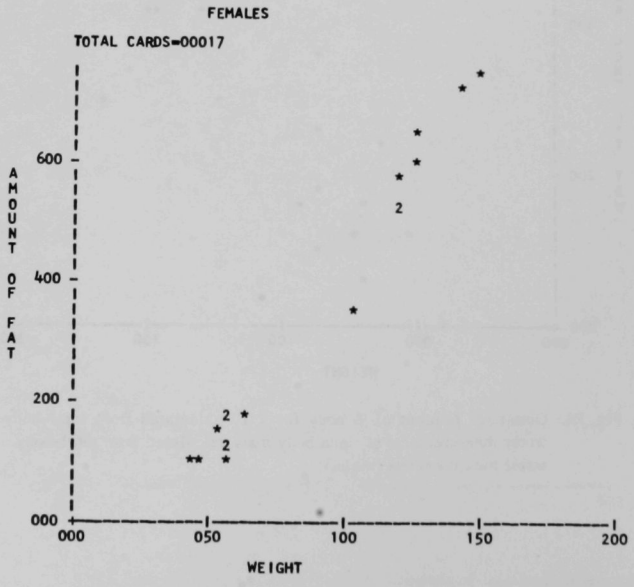

Fig. 24. Computer printout of (amount of fat in kilograms) x 10 (ordinate) vs. body weight in kilograms (abscissa) females

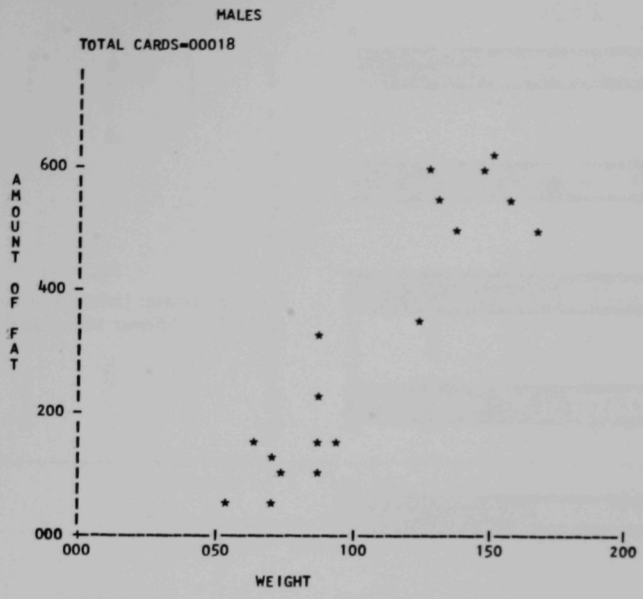

Fig. 25. Computer printout of (amount of fat in kilograms) x 10 (ordinate) vs. body weight in kilograms (abscissa) males

Potassium as an Estimator of Fat-Free Tissue or Muscle Mass

Can we use potassium as an estimator of fat-free tissue or muscle mass? Pearson,[13] in a recent review, cautiously concluded, "present methods do not provide precise compositional values." We agree and would like to review why potassium cannot be a reliable estimator. Investigators proposing these models have assumed the concentration of potassium in muscle is invariate and identical from muscle to muscle and from individual to individual. They have assumed the potassium content of other tissue is identical for all individuals. Neither of these assumptions is reasonable.[14] The potassium content of different muscles may differ by as much as 30% as reported by Lawrie and Pomeroy.[15] In addition, the potassium content of other tissues may vary radically as has been shown for the sheep erythrocyte.[16] The large variance of potassium for muscle from clinically healthy subjects is illustrated in Figure 26, which summarizes data accumulated by several laboratories including the laboratory of one of us (APR). Relating potassium to intracellular water does not improve the situation (Figure 27). What is the situation if one analyzes muscle from patients who are ill? It is evident that the variance is large when one examines potassium expressed as potassium/kg fat-free muscle (Figure 28), or potassium/liter of intracellular water (Figure 29).

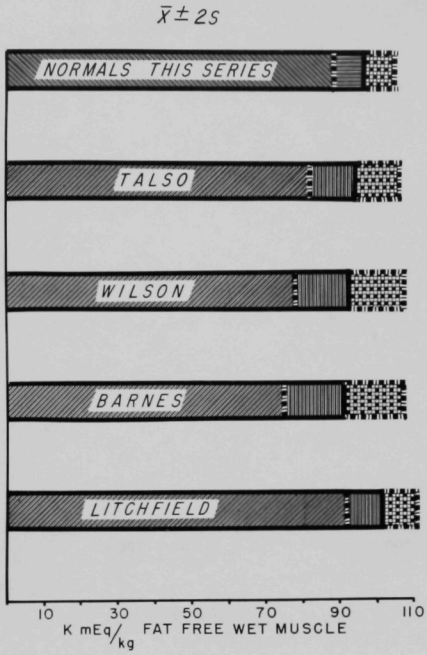

Fig. 26

Potassium content (mEq/kg) of fat-free muscle reported by different laboratories[10,24-27]

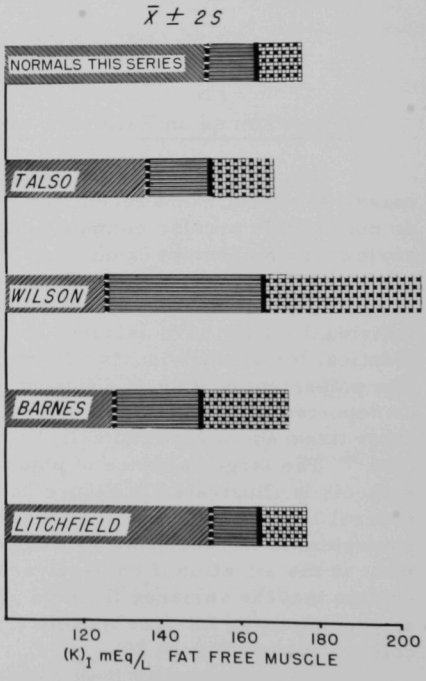

Fig. 27

Potassium content (mEq/l intracellular water) of muscle reported by different laboratories[10,24-27]

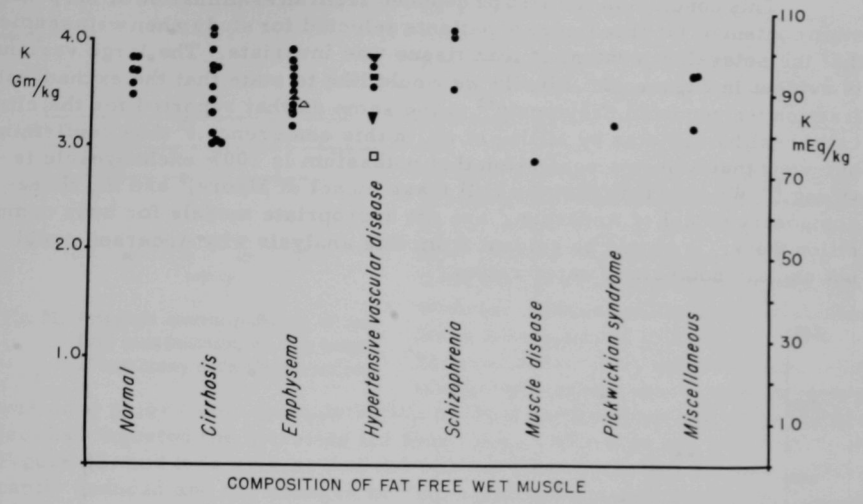

Fig. 28. Potassium content (mEq/kg) of fat-free muscle from patients with different diseases[10]

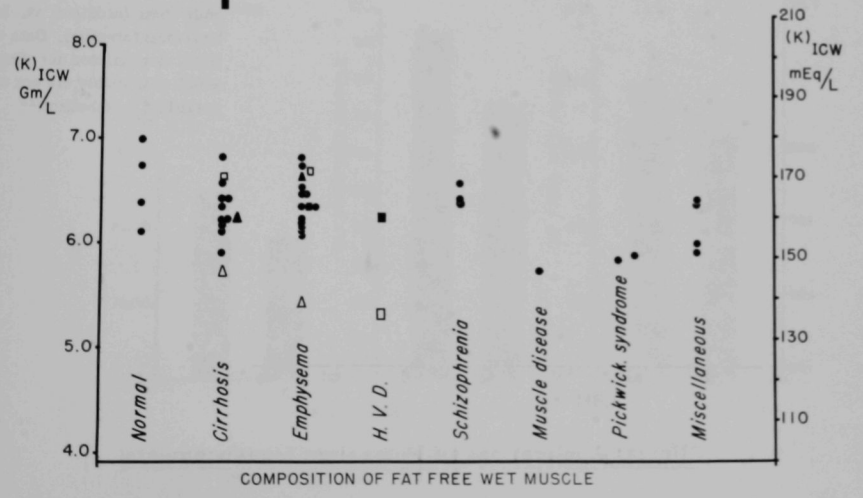

Fig. 29. Potassium content (mEq/l intracellular water) of muscle from patients with different diseases[10]

This conclusion can also be deduced from an examination of the potassium content of fat-free tissue of patients selected for study when we assumed that the potassium content of lean tissue was invariate. The large variance is evident in Figure 30. Finally we would like to state that the exchangeable fraction we reported previously[12] is the same as that reported for the clinically healthy subjects by Miller et al. in this conference,[17] thus confirming our view that Moore's contention that potassium is 100% exchangeable is wrong.[18] We conclude that the cell mass model of Moore,[3] and the three-component model of Anderson,[1] are not appropriate models for body composition work. It should be evident from this analysis why Anderson could not explain potassium/water ratios.[1]

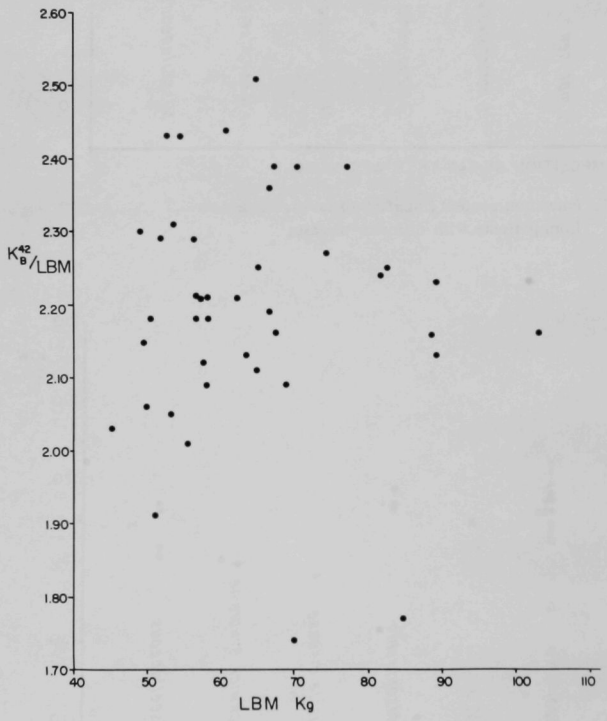

Fig. 30

Potassium content (g/kg) of lean body mass (ordinate) vs. lean body mass (abscissa). Data of patients hospitalized for diseases which presumably did not affect potassium metabolism.[19]

Clinical Applications of Potassium Measurements

Does this mean that potassium measurements are useless? No, it does not. If one knows one is studying a clinically healthy population and one knows that the experimental procedure is not going to affect the potassium concentration of fat-free tissue, then it is easy to show that the potassium content of lean tissue is stable and reproducible. Figure 31 illustrates

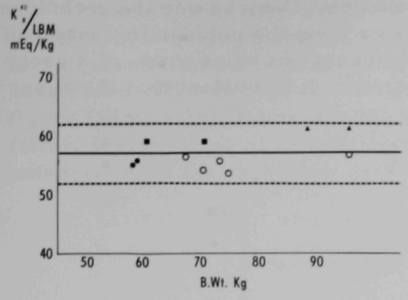

Fig. 31. Potassium content (mEq/kg) of lean body mass (ordinate) vs. body weight of ambulatory schizophrenic subjects

data derived from a study of an ambulatory population.[19] Replicate measurements are illustrated by the solid circles, squares, and triangles. Note that the potassium content of fat-free tissue did not change much despite a change in weight, and this is due to the fact that predominantly fat-free tissue was added. As we mentioned earlier, changes in the body content of potassium do indeed reflect changes in the potassium content of muscle. Potassium-depleting diuretics were administered to a subject with hypertension. Body potassium measurements were made, and a muscle biopsy was done prior to the administration of these medications and after the subject had ingested the diuretics for four weeks. The data are illustrated in Figure 32, and it is evident that the subject's body potassium was significantly reduced and the changes in $^{42}K_B$ reflected changes in muscle content of potassium and not of muscle mass or cell mass.[20]

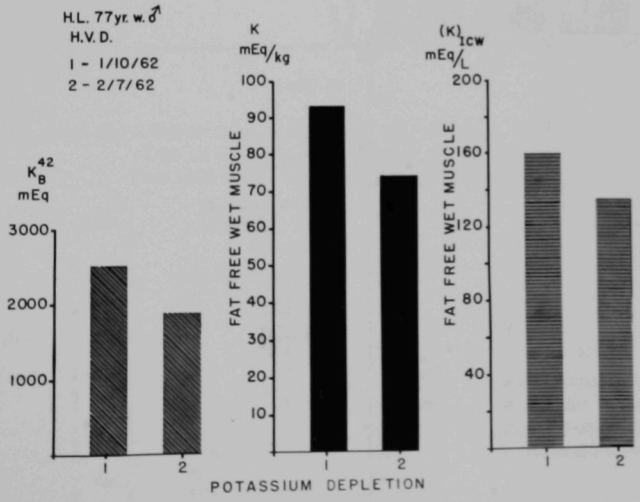

Fig. 32. Changes in body content of potassium and muscle content of potassium after administration of diuretics

Another illustration of the clinical usefulness of body potassium measurements in conjunction with other dilution techniques is apparent (Figure 33). It illustrates changes in body composition of a patient with acute poliomyelitis. The metabolism of potassium in this body was similar to the metabolism of women with this disease, and different from that of men.[21] Clinically his

course resembled the clinical course of women. One can use the technique to study the effect of pharmacological agents upon the potassium content of man. Figure 34 illustrates some measurements one of us made of a group of hypertensive subjects ingesting a diuretic.[22] It is evident that the agent depleted them of potassium.

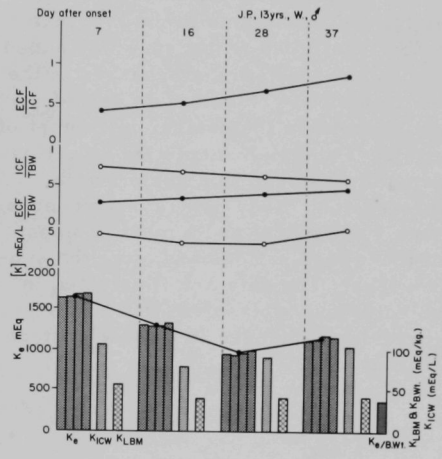

Fig. 33

Changes in total-body potassium (K_e), intracellular concentration of potassium (K_{ICW}) and lean body mass content of potassium (K_{LBM}) during the course of poliomyelitis. The measurements were made 7, 16, 28 and 37 days after the onset of the disease.

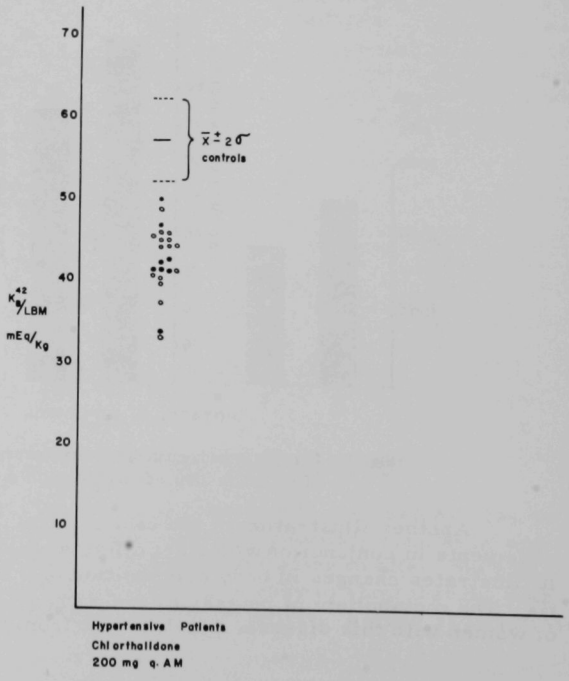

Fig. 34

Potassium content of lean body mass of subjects to whom potassium-depleting diuretics were administered

The limited time precludes further discussion of our data on the relationships between anthropometric measurements and potassium and fat. In a presentation during another conference the essayist stated that if you have more salt water you have more salt and more water,[23] and so the next figure (Figure 35) illustrates the fact that if you have more fat then you are fatter, irrespective of sex (Figure 36). Needless to say, this observation is independent of the technique used to estimate fat content.

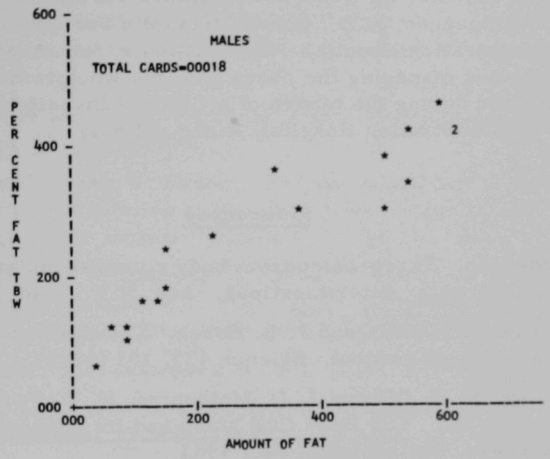

Fig. 35. Computer printout of (% fat) x 10 (ordinate) vs. (amount of fat in kilograms) x 10 (abscissa). Data calculated from total-body water measurements (males).

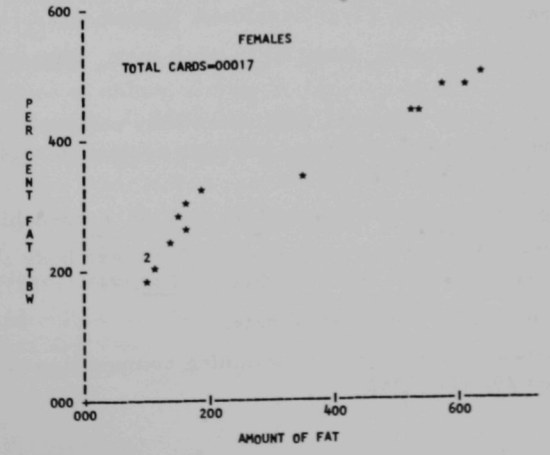

Fig. 36. Computer printout of (% fat) x 10 (ordinate) vs. (amount of fat in kilograms) x 10 (abscissa). Data calculated from total-body water measurements (females).

Acknowledgement

The authors would like to thank Arthur Johnson, Ph.D., Jack Bechtel, M.S. and Harold Schoolman, M.D., of the Biostatistics Research Support Center, Veterans Administration Hospital, Hines, Illinois, for assistance with the design of some of these experiments and analysis of the data; Joanna Wheeler, B.S., Research Coordinator, Veterans Administration Hospital, Hines, Illinois, for general assistance during the course of this study; and Herta Spencer, M.D., Chief, Metabolic Service, and her staff, Veterans Administration Hospital, Hines, Illinois, for cooperating with us by hospitalizing and managing the obese patients who starved. Some of these data were obtained during the tenure of a Clinical Investigatorship (APR) in the Veterans Administration Hospital, Hines, Illinois.

References

1. E. C. Anderson. Three-component body composition analysis based on potassium and water determinations. Ann. N.Y. Acad. Sci. 110, 189 (1963).
2. G. B. Forbes, G. Gallup and J. B. Hursh. Estimation of total body fat from potassium-40 content. Science 133, 101 (1961).
3. F. D. Moore, K. H. Olesen, J. D. McMurrey, H. V. Parker, M. R. Ball and C. M. Boyden. The Body Cell Mass and Its Supporting Environment. W. B. Saunders, Philadelphia, Pa., 1963.
4. P. J. Talso, C. E. Miller, A. J. Carballo and I. Vasquez. Exchangeable potassium as a parameter of body composition. Metabolism 9, 456 (1960).
5. W. Van Dobeln. Estimation of muscle mass of the human body from ^{40}K determination. Medd. Flyg. Navalmed. Namnd. 11, 1 (1962).
6. A. Keys and J. Brozek. Body fat in adult man. Physiol. Rev. 33, 245 (1953).
7. N. Pace and E. N. Rathbun. Studies on body composition. III. The body water and chemically combined nitrogen content in relation to fat content. J. Biol. Chem. 158, 685 (1945).
8. J. Brozek. Personal communication to A. P. Remenchik.
9. G. C. Pitts. Density and composition of the lean body compartment and its relation to fatness. Am. J. Physiol. 202, 445 (1962).
10. A. P. Remenchik. Unpublished data.
11. G. B. Forbes. Methods for determining composition of the human body. Pediatrics 29, 477 (1962).

12. A. P. Remenchik and C. E. Miller. The measurement of total body potassium in man and its relation to gross body composition. Whole Body Counting. International Atomic Energy Commission, Vienna, 1962, pp. 331-339.

13. A. M. Pearson. Body composition. Newer Methods of Nutritional Biochemistry, Vol. II, Ed., A. A. Albanese. Academic Press, New York, 1965, pp. 1-40.

14. C. T. G. Flear, R. G. Carpenter and I. Florence. Variability in the water, sodium, potassium and chloride content of human skeletal muscle. J. Clin. Path. 18, 74 (1965).

15. R. A. Lawrie and R. W. Pomeroy. Sodium and potassium in pig muscle. J. Agr. Sci. 61, 409 (1963).

16. M. S. Mounib and J. V. Evans. The potassium and sodium contents of sheep tissues in relation to the potassium content of the erythrocytes and the age of the animal. Biochem. J. 75, 77 (1960).

17. C. E. Miller, A. P. Remenchik and W. V. Kessler. Precision of assay of whole-body potassium in man. Body Composition. University of Missouri, Columbia, Missouri, 1967, in press; also this report.

18. F. D. Moore. Discussion. Ann. N.Y. Acad. Sci. 110, 211 (1963).

19. A. P. Remenchik and P. J. Talso. Body composition of schizophrenics. Arch. Gen. Psych. 13, 444 (1965).

20. A. P. Remenchik, C. E. Miller, P. J. Talso and E. O. Willoughby. Depletion of body potassium by diuretics. Circulation 33, 795 (1966).

21. A. P. Remenchik, J. Dyniewicz and J. Schoenberger. Changes in body composition during the course of acute anterior poliomyelitis. J. Lab. Clin. Med. 53, 195 (1959).

22. A. P. Remenchik and L. C. Johnston. Potassium depletion produced by administration of chlorthalidone to nonedematous patients with arterial hypertension. Am. J. Med. Sci. 252, 171 (1966).

23. E. A. Boling. Changes in body composition during illness and convalescence. Ann. N.Y. Acad. Sci. 110, 978 (1963).

24. B. A. Barnes, E. B. Gordon and O. Cope. Skeletal muscle analyses in health and in certain metabolic disorders. I. The method of analysis and the values in normal muscle. J. Clin. Invest. 32, 214 (1953).

25. J. A. Litchfield and R. Gaddie. The measurement of the phase distribution of water and electrolytes in skeletal muscle by the analysis of small samples. Clin. Sci. 17, 483 (1958).

26. P. J. Talso, N. Spafford and M. Blaw. The metabolism of water and electrolytes in congestive heart failure. I. The electrolyte and water content of normal human skeletal muscle. J. Lab. Clin. Med. 41, 281 (1953).

27. A. O. Wilson. Electrolyte content of muscle samples obtained at surgical operations. Brit. J. Surg. 43, 71 (1955).

PERSONAL REMINISCENCES OF THE EARLY HISTORY OF THE RADIUM EXTRACTION INDUSTRY IN THE U.S.A.*

Arthur L. Miller

Romance, humor, tragedy, headaches, and heartaches are found in the history of the radium industry.

Flannery Brothers was a well-established firm of undertakers. There were three brothers: James J., Joseph M. and John S.--I knew them all. About 1904, they obtained control of a specially designed stay bolt for locomotives and the Flannery Bolt Company was in business at Bridgeville, Pa. In seeking for the best steel to make these bolts, Joseph M. made a trip to the leading steel centers of the world and learned that traces of vanadium appeared to give Damascus swords and Soligen fencing foil blades a superior quality. Now get a source of vanadium. Carnotite $[K_2(UO_2)_2(VO_4)_2 \cdot 1\text{-}3H_2O \cdot UO_3]$ (named in honor of the President of France, Carnot) had been found in southwestern Colorado, so claims were staked or purchased. Seeking a more easily worked ore and a more ample supply of vanadium, they purchased some properties in the high Andes in Peru. James J. took charge of the financial ends (he was president of the Oakland Savings and Trust Company, founded largely to take care of Flannery interests), and Joseph M. took over sales, education, and promotion at which he was a whiz. John S. moaned to me that they were making money and names for themselves and he was left to "do the body snatching" and keep the sure thing (undertaking) a going concern.

Through their efforts, vanadium steel came into being and they, or rather J.M., sold Col. Goethals on using vanadium steel for the hinges of the gates, etc. at the Panama Canal. They pulled a "spectacular" with Henry Ford, who adopted vanadium steel for his buggies, thereby saving about 1200 lb in weight.

About 1909, a sister was diagnosed as having cancer, so to Europe goes J.M. to get some radium, glowing reports as to its curative power having been reported. Result: No radium to be had for love or money.

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*These reminiscences are based on a series of letters from the late Arthur L. Miller to John E. Rose in February and March, 1959. Arthur L. Miller (1892-1963) was a chemical engineer (B.S., Ch.E., 1914, Purdue) who was intimately involved in the early activities of the radium extraction industry in the United States. His records document his personal involvement in the extraction and purification of 45 g of radium in the period from 1914 to 1929. Much of his success was due to his enormous capacity for attention to detail and for meticulousness in laboratory procedures. His frequently colorful recollections constitute a set of fragmentary and unintended memoirs that are presented here as a contribution to the early history of the radium industry. They have been prepared and edited by Asher J. Finkel (HD) and John E. Rose (RPY).

"We have an ore supply in carnotite, so we will make it ourselves." Result: The Standard Chemical Company was organized in 1911 and the race was on. He both lost and won. The sister died before we produced any radium, but we were the world pioneer in the commercial production of radium and up to 1921, the largest producer. The first radium was produced in 1913, i.e., 2.1 g Radium Element. Talk about "guts" and optimism: take an ore that runs about 3 mg per metric ton and no known method of treating it; start from scratch and expect a happy conclusion!

Glenn Donald Kammer (B.S., Ch.E., 1912, U. of Pittsburgh) came shortly after graduation, followed shortly after, or about the same time, by Dr. Charles Herman Viol (B.S., 1907, Purdue; Ph.D., Chicago; studied under A. A. Michelson, Robert A. Millikan and Herbert N. McCoy). The story goes that a Dr. Schlesinger was brought from Heidelberg and Dr. Otto Brill was brought from Austria. Brill was reputed to be a Tartar and Splinter in the Thumb; he returned to Austria, and Viol took over as Director of Radium Research Laboratories. I got my "sheep hide" from Purdue, June 10, 1914, and was purported to be a B.S., Ch.E. I landed in Pittsburgh June 14th and was on the job Monday, June 15, 1914, and was continuously on the payroll until January 1, 1930. Henry Titus Koenig (U. of Pittsburgh, 1912) is reported to have been on the Staff 1912-1914; I never knew him but he may have been at the Mill when I came on. In 1915 he teamed up with Schlesinger as the Schlesinger Radium Company (Denver, Colorado), later named the Radium Company of Colorado.

When the Standard Chemical Company started there was a lot of confusion as to designation of radioactivity: Mache Units--times more active than uranium--mg of RaBr $2H_2O$--and what have you. So right off the bat we adopted the metric system from start to finish--it was metric tons, liters, milligrams or micrograms of Radium Element, regardless of form. We even invented a unit of our own, "MU" (mill unit or units) by which we expressed the radium content of ore and all solids as milligrams of Radium Element per metric ton. For solutions or liquids, we gave the total radium content in mg Radium Element if the total volume was known; if unknown, we gave it as micrograms of Radium Element per liter--"mikes/liter" written μ/l. Mill unit was spoken as so many MU, but generally written "Mt"--they were interchangeable and no misunderstanding as to meaning.

So that you have some idea that the "Research Laboratories" using the entire 5th floor of the then Vanadium Building (now Flannery Building) was not "window dressing," here is the staff:

Charles H. Viol	Director of Research
Glenn D. Kammer	Asst. Director
Arthur L. Miller	Asst. to Kammer
Lester V. Walker (Cornell?)	Gamma-ray measuring

Marcus A. Gordon (Cornell)	Alpha-ray (radium control lab--where the radium was kept under close tabs from the ore up to the finished product)
Hiram Campbell	Asst. to Gordon in preparing samples for assay
Charles Powers (Michigan)	Doing fractional crystallization (Powers was a Pittsburgh pharmacist)
Harry Frank (Michigan)	Doing fractional crystallization
Emil F. Krapf	Pharmacist: Radium drinking water, radium ampoules, etc.
Harvey A. Seil	Ph.D.
William H. Cameron	M.D.
B. R. Almquist	M.D.
Frederick Proescher	M.D., Pathologist

This latter group had at their disposal monkeys, rabbits, guinea pigs, rats, and mice, on which they conducted all sorts of experiments with radium internally and externally. I think they ran one poor monk through about everything from beriberi to TB--their job was to try and find out what radium would and would not do. Their activities were not entirely confined to "test animals." They treated persons with malignancies and even "took a crack" at stimulating healing of x-ray burns! A most sincere effort to get the facts. These activities were "in full bloom" when I landed in 1914.

* * *

If you are not familiar with the method we used to keep tab on the radium as it went from the mines to the finished product, read S. C. Lind's section of Bulletin 104--Mineral Technology 12 (Department of Interior, Bureau of Mines, 1915) on his "trick" electroscope and methods for assay of radium, for a real belly laugh. We had our own private method--give us a sample, wet or dry by 10 a.m. today and in 24 hours we would give you the figures, accuracy plus or minus 1%. With two electroscopes, a single operator could handle 4 samples per hour including all computations and bookkeeping, and if he did not, somebody wanted to know why! He could do that and get in 16 minutes per hour reading the current Saturday Evening Post. From 1914 to April 1925 (when we shut down this lab) we did over 44,700 samples. The largest month was April 1920 when 1,028 were handled (a short month, but we used 4 electroscopes and 2 operators).

We handled samples that varied all the way from 1 to 2,000 and better mg Radium Element per ton and solutions that were diluted better

than a millionfold. The method was OK as different operators using different 'scopes would check each other "on the nose." While we could use less, for nice fast reading we liked to have the (observed) sample carry 4×10^{-12} g of Radium Element fully aged. On overnight standing, the growth of radon (12-15% of max) from 0 to 25×10^{-9} g Radium Element gave a nice fast reading. This method was never published to my knowledge.

Madame Curie prepared the radium standard for the French government. The second one she made came to us. A small dab of bromide--glass tube ca. 10-12 mm long, with a rough seal on one end. The original value was 0.96 mg Radium Element. The third one went to the Bureau of Standards for their use; Dr. N. E. Dorsey set up the radium measuring, but before doing so he spent several days in Pittsburgh for instruction in the methods we had "cooked up." We used a 1/2-in. lead plate between the sample and the 'scope to try and make certain we were making a hard gamma-ray comparison. Lind used 3/8 in., and one "gal" at Memorial Hospital (New York City) used less in measuring some debris from a flask change--boy, what screwy results she gave me, until she was set straight on the lead thickness deal.

Early in the game a purity of 60 to 65% was deemed ample, until the thing was tilted to 68.8% on the 1150-mg batch of October 1914. We always finished as bromide and converted to sulfate. That October 24th, 1914 deal was just a fortuitous set of circumstances. Kammer, who had been doing all of the final purification, left August 1, 1914 for England with 4 g for delivery at several places in England (carried it in a hand bag!) but before they would accept delivery they had insisted that their Physical Laboratory at Teddington must examine, test and certify it was radium only--no mesothorium. Tubes had to be opened, resealed, etc. They gave him a "hard time" and with the war on, he was hung up through December of 1914. We had been accumulating stuff for Kammer to process, but there was no Kammer around. The Sales Department was hounding Viol for a firm date for shipping the orders on hand, all finished radium having been tubed and shipped. Viol discussed the matter with me, and I offered to "take a shot" at it. We set a date for finishing and an estimate as to what the number of mg would be. When the smoke cleared away he was very happy that I had made him a liar on both counts--beat the finished date, the amount by a wide margin and had upped the purity! You can have no idea as to how far a toad will jump, until you poke him.

* * *

The Standard Chemical operated or worked quite a number of claims in southwestern Colorado (mostly Montrose County), had some properties in eastern Utah. John I. Mullen was in charge of Colorado (all mines). Thomas R. Henehan (one time Commissioner of Mines, Colorado) was boss of the Mill Site (Joe Jr. Camp)--5 acres on which we had a concentration

mill, hydroelectric plant (3 phase 200 V), mines laboratory, commissary, etc. During the winter of 1916-1917 I was foreman of the mill--three shifts per day, 7 days per week, with responsibility for the lab (three shifts per day) and a hydroelectric power plant which had been designed to operate during the rainy season and high water--some sport to keep going--when all the San Miguel River would not provide enough water. We even tried to do the impossible: viz., take 4 four-cylinder automobile engines, belt them to a common shaft tied to the water turbine and keep all 5 synchronized--that is producing power the hard way.

The various groups of claims were: Jo Dandy, Monogram, Long Park, Shamrock Club (richest and nearest to the mill--about $1\frac{1}{2}$ miles), and Dolores (about 5 miles down the San Miguel River). Prospecting and exploration was conducted by core drilling (using hardened steel shot) and by diamond drilling, both of which required water, which was taken from Mill Site to location by burro train. A burro train consisted of one man (burro puncher) on horseback, a good "burro" dog and 15 head of burros. The company had over 300 burros ("Rocky Mountain canaries"). Martin Skees (boss burro puncher) knew them all by name, description, color, size, disposition, and the brands they carried besides our "lazy LJ." We used one string of 15 pack mules handled by a Pat Malloy for long and heavy hauls. This "water train" of 15 mules could transport 300 gal--two 10-gal cans per critter.

At the mill we had a pumping plant to hoist river water to a large storage tank about 150 ft above the mill. You really appreciate water, when you must carry it with you!

By 1921 over 6000 holes had been drilled, sampled, and mapped by our civil engineers. Where the overburden was $22\frac{1}{2}$ ft or less we used a "jackhammer" and "cisco steel" (hollow) for punching holes, with a gasoline engine driven air compressor. This started in 1915. Calyx core drilling was practiced from the very start. With the knowledge, within reason, of the location, depth, thickness, and values of the various ore bodies, a decision could be made as to probable best means to exploit same: open cut (?), tunnel (?), combination of both and best location for mine mouth. Generally such ore as was located was at about 6000 ft elevation.

Some claims were in such rugged locations that the ore had to be sacked (80 lb per) in the mine, dragged to the portal, and let down with block and tackle to a place where you could get to it by burro! On the average, each 2500 tons of stuff taken out was hand sorted to about 500 tons--the ore ran in color from light canary yellow to deep blue-black. An ore sorter at one place or mine was no good at another until he had become familiar with characteristics of the ore in that location. Most of them were "smart cookies"--they split every ore sample right down the middle, sent

one part to the lab and retained the other until they received the assay of uranium and vanadium. Then they studied the ore in the light of the assay. We also gave them an alpha-ray figure on radium content--which was an educated estimate and not a precise (control lab) figure. The better grade ore was shipped directly to Cannonsburg. Stuff running 1% U_3O_8 was known as "mill dirt" and went to the concentration mill; however, most of the stuff I got was about 0.85 to 0.95%. Under 1% went on the dump.

At the mill (Colorado), the "mill dirt" was handled as follows: crushed in "dry pan" (Chilean Mill), thence through a rotary kiln to lower the moisture to less than 1% (coal fired and the freight on coal was $20 per ton from the rail head--Placerville), thence through a ball mill--not to grind, but rotated at a speed where charge and grinding flints slid down the circumference (the idea, being to rub the carnotite off the sand grains with minimum breaking of the sand grains; the speed of rotation, feed speed, proportions of different sizes of balls (Swedish Flints) all had quite a bearing on result), thence through a Raymond impact pulverizer to knock the values out of the ore into an air stream and into a cyclone dust collector--the gangue being discharged to the dump.

The "values" were so fine that 90% was minus 200 mesh, which meant a double sack (inner paper--outer canvas) carefully tied for shipment. A freighter with 6 horses drawing 2 wagons (on line so that on a bad road, with mud or steep pitches, he could advance one wagon at a time) made the 65 miles to the railroad at Placerville (D.R.G. & W. narrow gauge). He could handle about $5\frac{1}{2}$ tons and it took a week (with good luck) to make the round trip. His pay: 20 bucks per ton--he furnished the gear, horses, feed, food and lodging. In some places there was no road or a reasonable facsimile of same. A water level road along the San Miguel River was under construction in 1916 and completed in 1917, when QUAD trucks began to replace horses. From Placerville the concentrates and/or ore went to Salida (Colorado), transferred to standard gauge and on to Cannonsburg to the mill (a revamped old stove factory) for chemical treatment.

The efficiency of the "dry process" was poor and we knew it, but until the experiments with a "wet process" showed such promise as to justify the design and erection of facilities to carry it out, we had no choice but to limp along. The "wet mill" was built early in 1917 and was in operation by the middle of July 1917. Materially cutting the power requirements, it eliminated the ball mill and the costly coal and rotary kiln. As to increased efficiency, I have no personal knowledge since I came back to Pittsburgh as it "started to roll." But I do know that the reworking of the tailings pile (stuff I put on the "dump") was quite fruitful. I was glad to see the ball mill go--we had worn out most of the usable supply of Swedish flints, and had resorted to the native flints we could find in and along the river for about a mile each way of the mill and the suitable "junk iron"

around the place. It was a great experience--if you did not have something, you looked to see what you could make it out of and what you could use as a substitute--often substituting for the substitute!

While the ore, etc., was never handled in batches that contained a gram of radium, for better understanding, I will give an outline as if such were the case. For 1 g (finished Radium Element) it took about 6 months from the mines to the finished product. The more than 200 men at the mines took out 2500 tons which was hand sorted to 500 tons--running about 1% U_3O_8--which was taken to the concentration mill at Joe Jr. Camp (on the San Miguel River) about 4 or 5 miles above the junction of San Miguel and Dolores Rivers. These 500 tons were concentrated to about 125 tons and hauled to Placerville for shipment to Cannonsburg for treatment. It took about 150 men a month, divided into 8 departments, to process this amount, using about 500 tons of chemicals, 1000 tons of coal and 10,000 tons of distilled water. The radium was checked into and out of each department.

Department 8 did the first series of fractional crystallizations, using a series of common porcelain bath tubs, heated with block tin steam coils immersed in the RaBaCa chloride solution--naturally the solution had to be neutral. The top 3 tubs took about 1000 liters, total, for the first step. The volume was determined with a calibrated 1- by 1-in. maple rod, equipped with a set screw to determine the top surface--the stick to rest on the outlet of the tub and held plumb, a fruitful source of error, when and if the bottom of the stick got worn or "brushy." "Tommie" Thomas in charge of Department 8 was coming up "short" and figures Joe Ambrose in Department 7 was rooking him on the measure. Joe was on the ball, when Tommie would call for more liquid, Joe's retort was "One poomp--wan liter--tausend poomps--tausend liter." The control laboratory, 30 miles away found the answer--the error was not a percentage one, but a constant volume one--Tommie's measuring rod had worn short and he was giving Joe credit for more liters than he was getting! Recalibration of the rod cleared the mystery.

By a "series" of fractional crystallizations the bulk was trimmed to about 100 kg RaBaCa chloride, the mother liquor tails being almost a saturated solution of $CaCl_2$. This was to be expected as the original ore carried considerable gypsum. The "heads" were put in solution, the volume measured and sampled, and then taken to dryness in a steam pan. They were then placed in large-mouth glass bottles, corked, put into suitable galvanized steel cans, with hinged locking top and carrying bail. Now hold your hat! Tommie and his helper, with a can in each hand brought them to the Pittsburgh Lab on the trolley! Probably a couple of hundred mg Ra! The stuff was put into solution, filtered, volume measured and samples taken--to be run for Ra and Ba content--Ba being reported as total weight barium sulfate in kg. By use of huge Royal Meissen porcelain

evaporating dishes over direct gas burners it was taken through a "series" involving crystallizations in acid solution. The "heads" went to the next room for further enrichment, etc.

Several schemes were used at the mill in working the ore or concentrates. Dr. Warren F. Bleeker had a scheme that was different from Louis Vogt's. There was considerable rivalry and feeling between the two, so Dr. Viol and I spent several days (nearly a week) as observers of a run a la Bleeker--expecting shenanigans. Doc took the day "watch," when both of them were around (11 hr), and I would relieve him and stand the night trick of 13 hr. No "funny" stuff was attempted, as far as I know, but we did see that samples were properly taken, weights and volumes correctly recorded, etc. This was the spring of 1915. We hired a room from Jim Henderson, a millman, who divested himself of the classic: "Take a rope up and cypher out that tank." We used the same bed--one out and the other in!

The concentrates were mixed with salt, roasted in a Wedge furnace, leached and treated to recover the radium, vanadium, and uranium, the latter being a "pain in the neck" at the time--only use for it was to color glass. Considerable work was done to produce ferrouranium (Standard Alloys Company was organized for the purpose). Later some uranium steel was made and a reversible pitch, aeroplane propeller was made by the Dicks-Luttrell Propeller Company (another Flannery project).

* * *

Luminous zinc sulfide was under research from the very start. England used stuff that carried 215 micrograms per gram for 'plane dials. They figured a plane only lasted about 30 hr in combat and they wanted high initial brightness. A Mr. Glew, in England, furnished some zinc sulfide and we the radium; we also furnished the activated zinc. In an effort to improve the quality of our zinc, J.M. imported an Englishman by the name of Whitehouse who was reputed to be a whiz at making the stuff. We installed him in the room a couple of doors from where Kammer and I were doing our research on the stuff. With our raw materials and reagents his stuff was lousy, and he blamed the raw materials, but "If he had the making from his favorite chemists shop in London, all would be well." It all came out when one day we received a shipment of zinc salts, reagents, etc., from England, which had been ordered by cable. On unpacking same, the good old name of Baker and Adamson hit me between the eyes! In our research we had established that using the same (?) reagents, some times the zinc sulfide was good and some times poor as regards to response to light and alpha rays. Hence there must be some impurity or impurities that either killed or cured. Kammer gave me quite an argument, but I contended (and demonstrated to him) that there was only one thing to do, viz: clean up the solution just prior to normal precipitation by doing a partial precipitation

(to remove most if not all the impurities from the zinc). Then add known impurities in known amounts and/or combinations. This would tell us what must be in and what must not. At the time, we were starting with zinc ammonium sulfate. A shipment had arrived with a bottle broken. With a broom and dust pan we swept it off the floor, excelsior, dirt and all, and put it into solution, filtered out the broken glass, etc., did a partial precipitation, filtered, added the activators and followed through. The result clinched the argument and partial precipitation became standard operation procedure from there on out.

We checked on about every metal in the periodic table from Al on down and found some that killed, some that appeared to do nix and that copper was imperative. We worked together on this deal--he would mess around with it for a couple of weeks, hit a plateau (while I was doing radium refining), then we would switch activities and I would take up where he had left off and carry on for a couple of weeks. Out of it all we came up with consistent quality zinc ranging (at will) in color from yellow to deep green, a yellow green being the best all-around color. Persistency and hard work had paid off. Incidentally, we were not letting Whitehouse in on our activities and one day, just out of "cussedness" we showed him about a 500-g bottle of our rejected material and he was amazed at the high quality of the stuff and wondered, "How in hell could he equal, much less exceed it, and why had he been brought over in the first place!" He departed soon.

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Spas, mineral springs, etc. have been purported to provide relief and curative power for many ailments--the spring waters examined by us never showed radium, but some did show radon. A "gismo" was built and installed in the Kane Hospital at Kane, Pennsylvania to make radon charged drinking water. With some radium in solution, glass tubing, stopcocks, etc., each day with a mechanical pump you could bubble the air in a closed system through the radium solution and a freshly iced volume of water. The idea was that each day one could pump the accumulated radon through the ice water for say 5 min, close the stopcocks to the radium solution, and drink the radon charged water.

I questioned how much radon would remain in the body after the radon cocktail, so, using "Kam" as a guinea pig, we took samples of his breath and measured the radon content. Then we took a measured (gamma ray) amount of radon in an implant and broke the same in a closed glass system circulating through ice water. He drank same and we sampled breath every 10 min. Elimination was very rapid. Then we repeated at a later date, but shortly before ingestion he chewed up and swallowed a number of willow charcoal tablets. Elimination was not so rapid and the bulk of it was nearly gone in 30 min, with almost zero retention at 4 hr.

I shudder when I think of the gallons of "Radium Drinking Water" we made and sold: 2 micrograms Ra in 50 cc (one dose)--put up in glass stoppered bottles--and even more--the 50 and 100 microgram (in 2 cc physiological salt solution) for intravenous injection!

The Radium Remedies Company (headquarters on (?) Federal Street, Pittsburgh) advertised extensively: Radium soaps, ointments, drinking water (?), radium elixir-of-life tablets. It even had a big exhibit at Exposition Hall (near the point in Pittsburgh). Since we were the only producers of radium we were curious as to their source of supply and radium content of their wares. Their deal to make radium drinking water involved a metal tube, with an eye in one end; put a thread through the eye, hang the tube in a quart bottle of water (must be tightly sealed--suggest use of type of bottle used to make root beer at home). Next day quickly drink the quart of water, refill, repeat next day, etc. I took in this exhibit and "made like a customer" and asked the pitchman, how can the radium get through the metal tube? Reply: Radium so powerful that if we had a concrete wall from Pittsburgh to Mexico, it would come through! He had a flock of testimonials from folks who could only afford a lead pencil and nickel tablet paper, but they were helped or cured of various and sundry ills. Next question: How much radium in tube? And how much cost? Reply: Cost--$100.00 cash or terms could be arranged at so much per week; radium content--in very impressive voice--one one-millionth of a gram! He could have killed me for my reply (he had a good crowd around): "Oh! At present prices--all of twelve cents' worth!"

A box of their radium elixir-of-life tablets was so low in radium content as to defy an accurate determination. Viol, in a talk to a group at Mellon Institute, had casually mentioned that we could measure with a 1% plus or minus accuracy, as little as 2 billionths of a gram of radium. The distinguished Dr. John A. Brashear (the astronomer and founder of Allegheny Observatory, Pittsburgh), who was present, opined, that Viol was an unmitigated liar--it just could not be done! With the aid of a number of our group, who made the rounds of several drug stores (buying one box of tablets at each), we collected a dozen or so boxes of the elixir-of-life tablets. It took "Hi" Campbell several days to "ash" same and prepare the lot as a sample. Result: Gordon reported that the radium content was about 10 times what would be found in the dust and dirt swept up off any paved street! Their stuff at least had this merit, it contained so little radium that it would do little or no damage, which is more than could be said of our ampoules and drinking water. I do not recall when we or they discontinued these items.

Publications

Papers

Miller, C. E., and A. J. Finkel. Radium Retention in Mice after Single Intravenous Injection. Radiation Res. 26, 269-286 (October 1965).

Remenchik, A. P., R. K. Hukkoo, and C. E. Miller. Determinations of Body Composition by Gamma Spectrometry. Developments in Applied Spectroscopy, Vol. 5. Plenum Press, New York, 1966, pp. 437-458.

Remenchik, A. P., C. E. Miller, P. J. Talso, and E. O. Willoughby. Depletion of Body Potassium by Diuretics. Circulation 33, 796-801 (May 1966).

Remenchik, A. P., and C. E. Miller. Whole-Body Counters. J. Am. Med. Assoc. 197, 117 (July 1966).

Maletskos, C. J., P. N. Dean, S. A. Lough, and C. E. Miller. Intercomparison of the Reliability of Body Cs^{137} Measurements on Human Beings. Health Phys. 13, 1307-1319 (December 1967); and TID-23740 U.S. Atomic Energy Commission, Division of Biology & Medicine, Washington, D.C., June 6, 1967, pp. 1-102.

Miller, C. E., A. J. Finkel, and N. B. Wright. Cesium-137 Retention in Mice of Different Ages. Proc. Soc. Exptl. Biol. Med. 128, 563-566 (June 1968).

Evans, R. D., A. J. Finkel, R. J. Hasterlik, A. T. Keane, R. J. Kolenkow, W. R. Neal, and M. M. Shanahan. The Risk of Bone Cancer in Man from Internally Deposited Radium. Brit. J. Radiol. 41, 391-393 (May 1968).

Abstracts

Newton, C., R. J. Hasterlik, and C. E. Miller. Computer Program for Optimal Crystal Placement in Total Body Counters. Radiation Res. 27, 524 (March 1966).

Hasterlik, R. J., A. J. Finkel, C. E. Miller, N. M. Strandjord, and G. E. Valvassori. Radiation Induced Neoplasia and Necrosis in the Mastoids and Paranasal Sinuses of Man, A Prospective Study. Radiation Res. 27, 491 (March 1966).

Miller, C. E., A. J. Finkel, and N. B. Wright. Cesium-137 Retention in Mice of Different Ages. Radiation Res. 27, 548 (March 1966).

Finkel, A. J., C. E. Miller, and R. J. Hasterlik. Correlation between Retrospective Estimates of Maximum Radium Body Burdens and Clinical Findings in Dial Painters 40 Years Later. Third Intern. Congr. of Radiation Research, Cortina, Italy, June 26-July 2, 1966, Abstracts of Papers, p. 84.

Hasterlik, R. J., A. J. Finkel, C. E. Miller, N. M. Strandjord, and G. E. Valvassori. Neoplasia and Necrosis in the Mastoids and Paranasal Sinuses of Radium Bearing Patients. Third Intern. Congr. of Radiation Research, Cortina, Italy, June 26-July 2, 1966, Abstracts of Papers, p. 105.

Maletskos, C. J., P. N. Dean, S. A. Lough, and C. E. Miller. Intercomparison of the Reliability of Cs^{137} Measurements on Human Beings. Health Phys. 12, 1169 (August 1966).

Miller, C. E. Half-Time of Inhaled Europium Mixture in Man. Radiation Res. 31, 541 (July 1967).

Miller, C. E., W. Kessler, and A. P. Remenchik. Precision and Accuracy of Assay in Whole-Body Counters of Radioactivity in Man. J. Nucl. Med. 8, 328 (April 1967).

Miller, C. E. ^{154}Eu Retention Patterns in Small Animals. Radiation Res. 34 (1968).

Finkel, A. J., C. E. Miller, and R. J. Hasterlik. Radium-induced Malignant Tumors in Man. Radiation Res. 34 (1968).